Expert Insights

Thought leaders from Cambrex discuss market opportunities, drug development challenges, pediatric medicines, and more

Please click the circles to navigate

Small Molecules, Sizable Market Opportunities

The Crystal Maze

Pediatric Formulation 101

Small Molecules, Sizable Market Opportunities

The small molecule drug development pipeline is booming! And with shrinking clinical trial cohorts (especially in oncology and orphan indications), smaller and virtual companies are now able to take candidates further than ever before.

Stephan Haitz, President, CDMO Sales & Marketing at Cambrex

Often, it feels that statements such as, "Although small molecules remain the largest portion of the pharma industry, they are on the decline, with large molecules and advanced medicines set to dominate in the coming years" are the prevailing narrative in the industry. But does it stand up to scrutiny?

Looking at market data, the number of small molecules being developed as drug candidates has increased over the past five years (see Table 1). The growing number of preclinical candidates coming into existence has boosted pipelines, and there are more phase I trials taking place than ever before, with more than 7,300 launched or entering development over the past five years. In addition, 479 potential drug compounds advanced from one clinical development phase to the next in 2019, suggesting that the industry is continuing to invest in small molecule drugs – particularly in areas such as oncology and orphan diseases.

Big opportunities for small companies

There is a growing trend for smaller and virtual companies to push projects further through the development pipeline than they typically would have in the past. For example, 65 percent of clinical pipeline projects are now sponsored by small companies (see Figure 1). Previously, the high costs of clinical trials meant that only the larger companies had the resources to support late-stage development, including final drug product approval. Now, with the clinical pipeline continuing to focus on smaller patient clinical trial cohorts requiring fewer resources, smaller and virtual companies have

LINKS

e-book
Small Molecules: 2020 Vision

Sponsored by Cambrex | *Produced by* the Medicine Maker

the resources to support late-phase trials. They may, in some cases, even be able to commercialize these assets.

Another positive sign of the health of the small molecule sector is the amount of venture capital funding available, which includes investment for the early-stage life science companies that are developing the majority of new chemical entities (NCEs). In fact, in 2019, experts estimated that more than $23 billion was raised in IPO funding, follow-on funding, private investment in public equity, as well as venture capital and funding from other sources. Of this, $16 billion was in the form of venture capital funding for start-ups and early-stage companies.

The large and growing small molecule API market (5% growth in 2019) is also characterized by increased outsourcing, particularly by small and virtual pharmaceutical companies; despite the increased draw of biologics and cell-based therapies, the small molecule market remains an attractive business area for contract development and manufacturing organizations (CDMOs).

With the pharmaceutical industry currently focusing more on the quality of the drug product rather than on cost – as it had in the years since the turn of the century – drug companies are now returning to Western CDMOs for the manufacture of drug candidates and drug substances. These trends, as well as the industry's growing and fast-moving clinical pipeline and the highest FDA approval rate since the 1990s, are the reasons for the considerable optimism now found throughout the drug development sector.

Orphan drugs and the oncology scene

A total of 42 NCEs were approved in 2018, and 38 in 2019 – an increase on the average of 25-35 NCE annual approvals seen in recent years. And looking at the broader commercial market (beyond approvals), consumption data for all small molecule prescription drugs in seven major markets (US, UK, France, Germany, Spain, Italy and Japan) shows a total volume of 3,500 metric tons with an annual growth of around 100-200 additional metric tons of API each year. This includes continued growth of the large, 100-ton-plus, high-prevalence-disease sector, as well as of the 10-20 ton range representing the more targeted therapies, including orphan drugs.

Another recent trend is increasing investments by CDMOs in facilities for the manufacture of highly potent APIs (HPAPIs). The number of small molecule cancer treatments in development is a good indicator of the robustness of the HPAPI sector as a whole (most HPAPIs are being developed for the oncology sector). Overall, the small molecule oncology pipeline is growing well, now accounting for 38 percent of small molecule drug candidates in preclinical development, 35 percent of clinical-stage small molecules, and one third of recent FDA approvals. Revenue and volume data for the 252 oncology drugs on the market or in registration in 2019 shows a market value of almost $53 billion and a volume of 920 tons – significant compared with the typical commercial API volumes of around five tons per molecule.

CDMOs have reacted to these market trends by building in capacity on the assumption that all oncology drugs are highly potent with Operational Exposure Limits (OELs) in the 1-10 µg/m3 range. This is, therefore, an area of considerable interest for CDMOs given their expertise in handling such high-potency products and the current preference of the pharmaceutical industry for using Western suppliers.

In summary, small molecule drug development and manufacturing is not declining – on the contrary! We see more drugs at the clinical and preclinical stage than ever before, with record numbers of patients being prescribed small molecule drugs, for a wider range of conditions. Highly-potent products, especially in oncology and orphan indications, are particularly strong today. This is good news for the CDMO sector, which is benefiting from the demand for fully integrated services and experience with HPAPIs, and for small and virtual companies, which are able to take therapies further than ever before.

	2014	2015	2016	2017	2018	2019	CAGR (14-19)
Preclinical	2,272	2,682	3,001	3,187	3,170	3,581	9.5%
Phase I Clinical Trial	631	694	792	829	877	940	8.3%
Phase II Clinical Trial	731	784	816	848	910	919	4.7%
Phase III Clinical Trial	192	211	257	277	265	291	8.7%
Total Clinical Pipeline	1,554	1,689	1,865	1,954	2,052	2,150	6.7%
Pre-Reg/Reg	57	47	55	66	75	65	2.7%
Launched	1,438	1,478	1,507	1,528	1,559	1,596	2.1%
Total Commercial Pipeline	1,495	1,525	1,562	1,594	1,634	1,661	2.1%
Total	5,321	5,896	6,428	6,735	6,856	7,392	6.8%

Table 1: Small molecule New Chemical Entities (NCEs) pipeline 2014-2019 (data from Cambrex/Citeline).

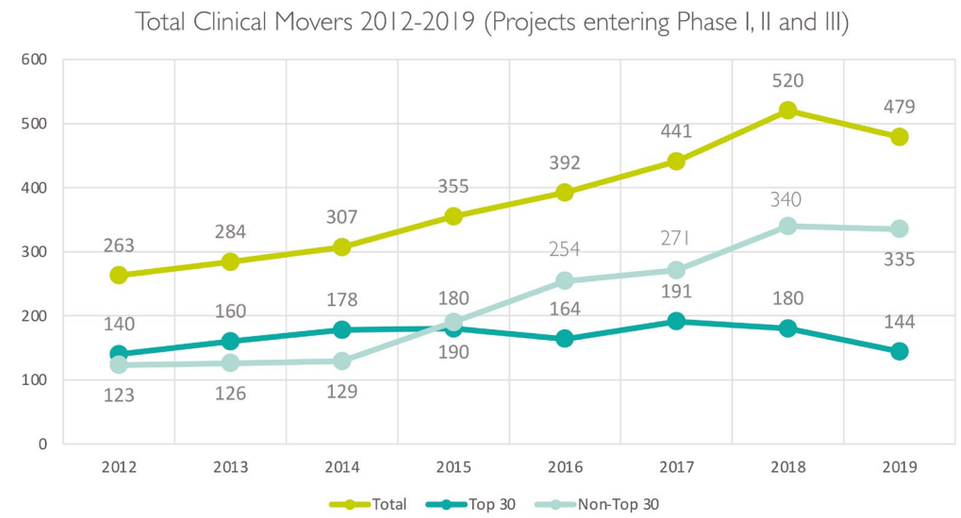


Figure 1: Total small molecule clinical movers 2012-2019 (data from Cambrex/Citeline).

LINKS

e-book
Small Molecules: 2020 Vision

The Crystal Maze

Unexpected hydrates of an API can cause a frustrating detour in the drug development pathway – the right analysis (and expertise) can help manufacturers find their way

David Pearson, Chief Scientific Officer at Cambrex Edinburgh, UK

Despite having modern modeling software, cloud-based computing, and an arsenal of analytical protocols at their disposal, predicting the crystalline nature of an API in its solid state remains a trying task for pharmaceutical manufacturers. This is particularly true of hydrates – APIs whose crystal structure contains water molecules. Up to 75 percent of all pharmaceutical compounds form hydrates during the manufacturing process, affecting many of the physicochemical properties of an active ingredient (1).

This is a sticking point for companies wanting to move their API through the clinical pipeline as quickly as possible as it challenges their ability to discern the overall bioavailability, physicochemical properties and intellectual property position of their material early in the development process. To help overcome these hurdles, larger pharmaceutical companies are increasingly turning to CDMOs to perform solid-state analyses in expert laboratories. Valued in excess of $150 million, CDMOs represent over 50 percent of the total market share for solid-state services (2).

Companies should perform comprehensive experimental screening of materials using a variety of solvents, experimental conditions, and processes, along with all the associated analytical techniques. Ultimately, you are looking for a robust solid form of a molecule that allows high-quality materials to be consistently delivered.

But inadvertent changes to the solid form of an API between batches can still occur. So how can companies effectively manage the variability in their manufacturing processes? Identifying and understanding the formation of alternative structures early on can reduce potential risks.

Hydrates: putting development at risk

Unlike solvated forms of an API, which contain organic molecules (such as ethanol) in their crystal lattice structure, hydrate formation relies on water and is not easily recognized during screening. As the vapor pressure of water is above zero, hydration and rehydration can occur in ambient conditions such as storage. If a drug were dosed in an anhydrous form that converts during storage or in the body to a lower-solubility hydrated form, for example, it may affect the observed solubility and dissolution of the API, making in vitro/ in vivo correlation more difficult.

If the potential to form hydrates is flagged to the development team early on, they can take steps to mitigate the risk. What does this look like in practice? We used polymorph screening to examine

LINKS

Webinar
De-risking the solid form landscape of an API

Sponsored by Cambrex | *Produced by* the Medicine Maker

		Water Activity In Ethanol									
		0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
Input Form	Form 1											
	Form 2											
	Form 3											
	Form 4											

Form 1 *Anyhdrous Racemate*
Form 2 *Hydrated Racemate*
Form 3 *Anyhdrous Conglomerate*
Form 4 *Hydrated Conglomerate*

Table 1: Small molecule New Chemical Entities (NCEs) pipeline 2014-2019 (data from Cambrex/Citeline).

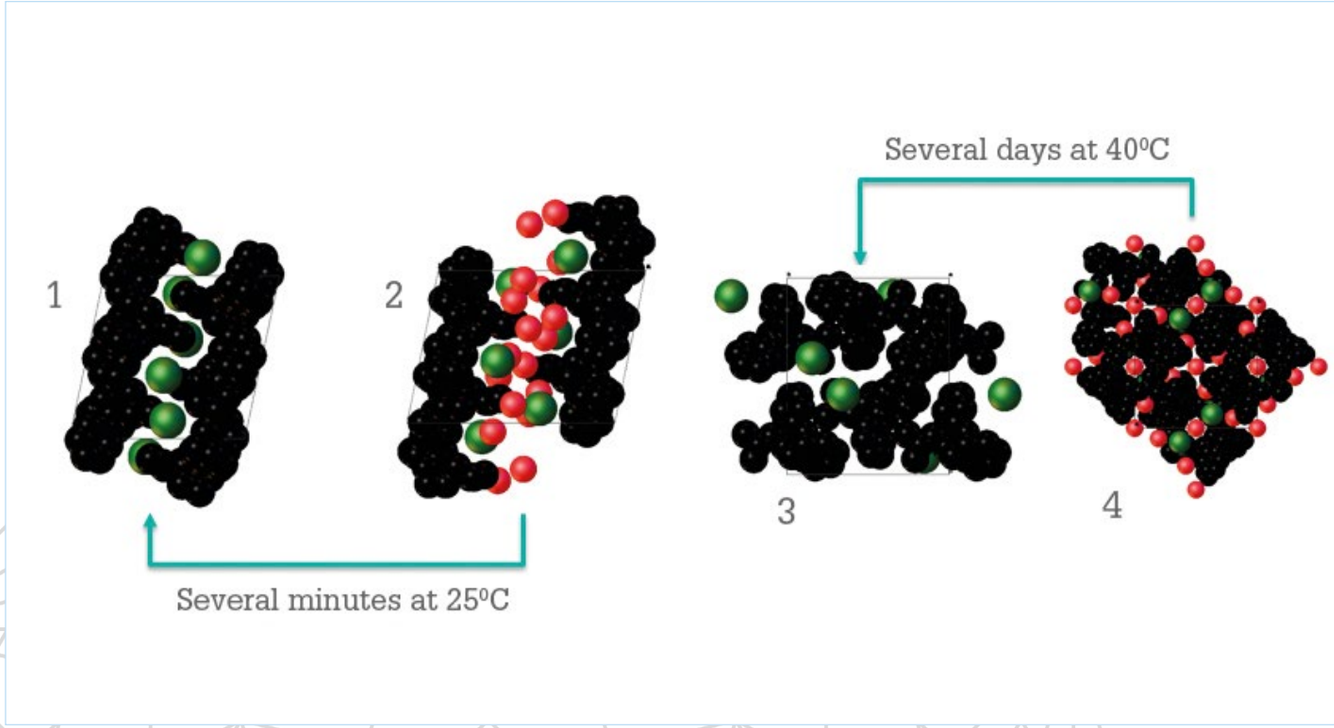


Figure 1. Different structures of API – different dehydration rates.

the difference in four different crystal forms of an API obtained from organic solvent and solvent/water mixtures.
The various solid forms included:

- Form 1 – anhydrous racemate and the desired form of the API
- Form 2 – a hydrated racemate
- Form 3 – anhydrous conglomerate
- Form 4 – a hydrated conglomerate

The rate at which these hydrated forms dehydrated varied massively – from several minutes under ambient conditions, to several days at 40°C in a stability oven (Figure 1).

Hydrate mapping, in which the water activity in organic solvent systems is systematically altered using varying volumes of water, is a powerful technique to understand the hydrate formulation in solvent-based systems. While DVS and variable humidity XRPD can provide a wealth of information on critical water activities and kinetics, a more practical method is solvent-based and closely related to real-world scale-up. Table 1 shows the results from the hydrate mapping for this particular API and its four forms.

We recognized that there were a variety of ways of obtaining metastable zone width measurements, or solubility data, using tools such as focused beam reflectance measurement (FBRM), turbidity

LINKS

Information
Peptide crystallization

Case Study
Selective crystallization of a novel polymorph

Sponsored by Cambrex
Produced by the Medicine Maker

probes, Crystal16 and the recent BlazeMetrics probes. In this case, a cooling crystallization was used and the metastable zone width measured in a variety of different solvent systems. This data was also used to give an early indication of particle size, morphology, and other properties. The ethanol-heptane system gave the widest metastable zone width, which allowed greater flexibility over the seeding point and de-supersaturation rates. The crystal form produced from these experiments was also checked and found to be the desired form 1, even without the use of seeds.

Once the solvent system was identified – and in this case, ethanol:heptane looked ideal – crystallization was optimized with an in situ, real-time analysis of the process. Using a BlazeMetrics probe, particles were monitored as they were produced and this provided a wealth of information on the formation, growth, morphology, and size distribution. The large particles obtained filtered very rapidly, dried easily, and ultimately gave a high-quality product and a process that could easily scale to a vessel size in excess of 1,000 liters.

Online Raman spectroscopy was not required in this case because the use of a non-aqueous solvent system reduced the risk of hydrate formation. However, it can be used to observe the formation of an undesired crystal form or, more importantly, confirm that there is no change in form occurring within the vessel during the crystallization process.

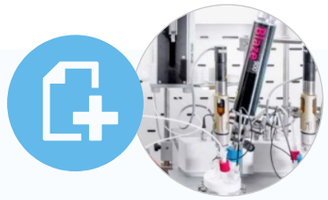
Importantly, our work shows how an understanding of the different crystal forms informs the selection of appropriate protocols. This will ultimately help accelerate the development of an API, reduce risk in the development and manufacture of both the drug substance and drug product, as well as adding intellectual property to the portfolio.

References

1. *J Christholm et al., "Knowledge-based approaches to crystal design," Cryst Eng Comm, 8,11 (2006).*
2. *Cambrex Marketing & Intelligence; (2019).*

LINKS

Case Study
Crystallization process development



Case Study
Crystallization process development 2

Sponsored by Cambrex

Produced by the Medicine Maker

Pediatric Formulation 101

The industry must move away from a "one-size-fits-all" approach when it comes to patients of any age

Ralph N. Landau, Head of Development at Cambrex Whippany, New Jersey

The pediatric population is one group that has benefited from the industry's goal of becoming more patient-centric and, over the past 20 years, has seen gradual improvement in the number and quality of drugs available to them. In fact, over the course of the past two decades, there has been a five-fold increase in the number of pediatric drug approvals (according to Cambrex Market Intelligence, approvals increased from 10-20 per year to 50-70 annual approvals today).

Regulatory bodies are constantly working to update their guidelines regarding the implications of drug substances and excipients for pediatric patients. In the USA, Congress has passed several acts to accommodate pediatric drug development including:

- 1997 – the FDA Modernization Act (FDAMA) provided marketing incentives to manufacturers who conduct studies of drugs in children. It gave companies six months exclusivity in return for conducting pediatric studies.
- 2002 – the Best Pharmaceuticals for Children Act (BPCA) reauthorized a provision that was originally contained in FDAMA.
- 2003 – the Pediatric Research Equity Act (PREA) requires the pediatric assessments of new drug and biologic licensing applications for all new active ingredients, indications, dosage forms, dosing regimens, and routes of administration.
- 2007 – the FDA Amendments Act (FDAAA) requires that the FDA track and make publicly available certain pediatric information resulting from pediatric clinical trials.

LINKS

White Paper
Pediatric dosage forms

Sponsored by Cambrex | *Produced by* the Medicine Maker

These acts provide structure and guidance to companies developing drugs for use in children, as well as some incentives, such as a six-month extension of exclusivity on existing formulations if adequate pediatric studies are performed. PREA allows the FDA to require a pediatric formulation of a drug and the studies conducted must use appropriate formulations for each age group. The PREA Act is triggered by one or more of the following criteria: a new indication, new dosage form, new dosing regimen, new route administration, or new API. The drug application must include a pediatric assessment unless the applicant has obtained a waiver or deferral.

Globally, agencies, such as the EMA, Health Canada and Australia's Therapeutic Goods Administration, also offer pediatric drug development guidance and regulatory requirements. If a company develops a pediatric drug product and receives approval from a USA regulatory agency and then wants to expand to Europe, for example, a separate submission for EMA regulatory agencies would be required for approval. The requirements vary somewhat by jurisdiction, therefore when developing a formulation intended for multiple jurisdictions, all requirements must be integrated into the development program.

On an international scale, however, regulatory bodies are demonstrating their desire to bolster the pediatric drug pipeline and are encouraging companies to find solutions for this patient group. In short, the problem of developing medicines for children can no longer be ignored.

Patient centricity

When developing medicines for the diverse population of pediatric patients, it's always best to establish what the requirements of the patient are in the particular therapeutic area. The most popular drug formats for treating pediatric patients are usually:

- oral liquid formulations
- oral solid dosage (OSD) formulations, particularly fast-dissolving or chewable tablets, or capsules
- multi-particulate formulations, such as mini-tablets and stick packs
- alternative oral delivery of liquid formulations via Medibottles and dose sipping

Liquid formulations are perhaps the most common approach as they bypass some of the issues associated with OSDs, but they do have their own constraints. For example, products in this format

LINKS

Webinar

Pediatric dosage form development – challenges and opportunities

Sponsored by Cambrex

Produced by the Medicine Maker

are often much less stable when compared with OSDs, leading to a shorter shelf-life. The use of multiple-dose bottles to dispense them also introduces the risk of micro-contamination. For parents trying to administer the medicine to children, there is also the challenge of getting the child to swallow the liquid rather than spit it out! Taste masking can also be challenging with liquids, but can be helped with particle coating. By adding pH-dependent coatings to liquid formulations prior to their suspension, the liquid will not possess the taste of the API. The API will become available as the pH conditions in the GI tract erode the coating.

As new dosage forms, such as stick packs, become available, they open opportunities for companies seeking improved ways to deliver their products to pediatric patients. Stick packs are convenient to administer and also come with the advantage of making a medicine look far less like a medicine – an aspect that can encourage, in particular, pediatric patient compliance.

There is also continuing interest in fixed dose combination approaches, where more than one drug is combined into a single drug product. These products improve patient compliance by reducing polypharmacy issues, but can be even more challenging to design for pediatrics because drug-dosing recommendations may not be suitable across all weight or age groups. However, companies are now finding ways to successfully adapt these formulations so that they work well across different age groups.

Another crucial challenge for pediatric drug formulators lies in identifying safe ingredients. Importantly, while many excipients are considered safe in adult populations, the data for their use in pediatrics is either scarce or non-existent. The FDA is now expecting safety work to be done in pediatric populations for all excipients used, helping to improve the quality of medicines designed for children. Again, keep in mind that acceptance of certain excipients for pediatric products may vary by regulatory authority. Pediatric formulations must address the differences between adults and children. For example, it is not just body weight that drives dosing. Children's metabolism differs from adults. An extended release drug product may behave much differently in pediatric populations; formulators must consider this in their design. Notable differences between pediatric patients and adults include:

- Metabolic rate is higher
- Intravascular and extracellular fluid compartments are relatively larger
- Protein binding is decreased
- Infants have proportionately higher total body water
- Each of which have the potential to affect drug performance and ultimately, influence the final drug product formulation.

The ideal medicine

What does the ideal pediatric medicine look like? In my view, the ideal formulation has yet to be developed, but I think that we're well on our way to seeing it happen. In 2020, there are more than 1,300 clinical trials underway investigating over 600 drug substances for pediatric use – a clear indicator of the industry's progress. To maintain momentum and demonstrate that we, as an industry, are developing drugs that are appropriate for the pediatric population, we must conduct robust clinical trials with clear endpoints.

At the same time, it is important to remember how a deeper consideration for the best dosage forms for children and true patient centricity can also benefit other vulnerable patient groups. End users who have difficulty consuming traditional medications, such as stroke patients, those with degenerative diseases like Parkinson's and Alzheimer's, or the elderly, can all benefit from formulations that take the stress out of the drug administration process.

LINKS

Case Study
Pediatric dosage formulation

Sponsored by Cambrex

Produced by the Medicine Maker