Where do CMOs like Cambrex need to invest?

Innovation in the small molecule drug industry is at an all-time high. In 2015, the US FDA approvals for new chemical entities (NCEs) were at their highest level since 1999. There are more chemical molecules in every phase of drug development than ever before when looking back over the last 15 years. With an increased number of new small molecules reaching the market and a growing pipeline in clinical research, the importance of chemical-based therapeutics to the pharmaceutical market has never been more prominent.

During this same time period, small molecules have also shown their great versatility in treating diseases. They have evolved from global blockbusters, treating millions of patients with chronic conditions, to more targeted therapies for oncology or orphan indications – where previously patients were living with debilitating diseases without treatment option.

The broadening landscape of small molecules in new therapeutic indications presents changing requirements from its supply chain – in particular manufacturers of active pharmaceutical ingredients (APIs) and intermediates. Chemical manufacturing assets need to be sufficiently flexible to produce APIs ranging from kilogramme to metric tonne quantities.

In this webinar we present a condensed review of the last 15 years of launched small molecules with regards to market consumption and resulting volumes of API and how CMOs need to be investing in their manufacturing assets to be able to supply pharmaceutical innovators with the required volumes. We finish with two examples of how Cambrex is monitoring the demand and investing the right capacity to satisfy customer needs as small molecules continue to evolve.
Contributors

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Joshua Van Kley is the Sales Operations Manager for Cambrex Charles City, Iowa, USA. Since 2008, he has been working with clients to determine API project needs, defining gaps, and delivering proposals which provide detailed solutions, timings and pricing. Joshua holds an Economics degree, and minor in Chemistry, from the University of Northern Iowa.

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Bjarne Sandberg is the Managing Director of Cambrex Karlskoga site and has managed the site since 2013. Prior to his current position, Bjarne has held a number of roles in Cambrex including Vice President Business Improvement and Finance, Business Unit Controller and Finance Director. Bjarne has been instrumental in the improvement and expansion of the Cambrex Karlskoga site over the past 10 years. He has more than 20 years’ experience in the industry including both commercial and operations. Prior to joining Cambrex he worked for Procter & Gamble. Bjarne holds a MsC in Industrial Engineering and Management from the University in Lulea.
Growing pipeline of small molecules

The last two decades have been a period of major change in the pharmaceutical manufacturing sector. Factors including the end of the traditional blockbuster model, the patent cliff, the burgeoning biologics sector, and the shift to niche patient populations and more targeted therapies, have all contributed to a drive for change amongst drug makers and contract manufacturers alike.

Determining how to react to these trends with a sustainable business model that is flexible enough to anticipate the events of the coming years, is one of the major challenges faced by Cambrex and other global contract manufacturing organizations (CMOs).

To assess the future needs of the industry, Cambrex undertook an extensive research project throughout 2016 to study the evolution of the small molecule market, particularly in terms of volume demand, FDA approvals and industry lifecycle.

Once the data had been collated and assessed, it became apparent that despite the tendency for biologics to be stealing the headlines, small molecule drugs continued to form the backbone of the pharmaceutical industry. Not only is innovation in the small molecule sector at an all-time high, the level of US FDA approvals for new molecular entities (NMEs) in 2015 was at its highest since 1999 (figure 1).

Of the 45 NMEs approved in 2015, by far the largest proportion - 33 out of 45 - were small molecules, while only 12 were biologics. Furthermore, there are more small molecules in every phase of drug development than at any point in the last 15 years (figure 2).
After removing monoclonal antibodies, recombinant proteins, peptides, as well as the non-new chemical entities (NCEs) such as line extensions or reformulations, figure 2 shows the increase in small molecules across all phases of drug development.

That said, a large pipeline does not necessarily mean a dynamic one. So, the next question to understand was whether the molecules were stuck in those development phases or were they actually moving through at healthy pace? In table 1 below, this analysis helps visualize how dynamic the pipeline is.

### Table 1

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Looking at phase I, in 2015 there were 177 new entrants that entered phase I from preclinical development. This compares to 168 during 2014 and 133 in 2013, so we can conclude that the pace of new entrants appears to be increasing. The same trend is true for projects moving into phase II and phase III.

A closer analysis of the NME approvals in 2015 showed that 21 out of the 45 were approved to treat orphan diseases – rare conditions that affect 200,000 or fewer Americans and for which there are typically few or no drugs available. It was also apparent that expedited review processes are being used more routinely, with 27 of the NMEs designated in one or more categories of Fast Track, Breakthrough, Priority Review, and/or Accelerated Approval. A third conclusion is that most launches take place in the US – 29 out of 45 of the new drugs were approved by the US FDA before receiving approval in any other country.

Historically, small molecule development was strictly focused on the search for the classic “blockbuster”, used to treat millions of patients with chronic conditions. More recently the versatility of small molecules has allowed the model to evolve towards their extension into more targeted therapies. This is especially relevant for orphan indications and oncology therapies. Our research data indicates just how significant this change has been: in 1999-2000 the average patient population targeted was 13 million, representing indications such as obesity, diabetes, conjunctivitis, gastroesophageal reflux disease (GERD) and hyperlipidemia, but by 2014/15 this had fallen to just 6 million as the drugs are being used for conditions such as multiple myeloma, cystic fibrosis and thyroid cancer.

Once we were able to establish the dominant trends, our aim was to use this to guide our investment strategy to ensure we had the necessary flexibility in both capacity and capabilities going forward.

### Study Methodology

To track the evolution of APIs by volume demand, we looked at the 408 small molecule drugs launched in the US over the last 15 years. An interval period of five years was chosen to give enough data points for a quantitative study and data from two consecutive years was combined to dampen any annual anomalies. This resulted in a final data set of 209 small molecules – around half the total number of approvals – which we believe was sufficient to identify emerging trends.

The study was focused on the US market to exclude potentially misleading data arising from differences in disease prevalence/epidemiology in more populous markets such as India and China that can result in large uptake of certain products which would preclude the classic product lifecycle typically associated with a commercial medicine. However, it can be assumed that volumes for the five major European markets and Japan would be similar to those recorded in the US. It is also important to remember that the research looked at NCEs only, and did not take into account reformulations, Abbreviated New Drug Applications (ANDAs) or line extensions.

Potential sources of error were also assessed, such as the effect both of mature products and of those launched in 2014-2015 that have yet to reach peak volume. We zeroed in on 16 particular products that it was believed would be the greatest source of error and repeated the analysis several times; however, the differences in the data were not significant and we therefore felt this approach was robust enough to allow any potential trends to be observed.
Results and key findings

- From an analysis of 209 of the 408 new chemical entities launched in the US during the last 15 years, peak API volumes appear to have evolved.

- For the US market, forecasted volume data for 2014-15 NCEs corresponds to a range centered around 10kg-10MT of API. By comparison, in 1999-00 the range was broader (1kg-100MT).

- 12 of 27 products from 2014-2015 are expected to be around 1MT volume at peak in the US.

- When including the 6 additional major markets (5EU and Japan), volumes will be approximately the same as the US.

- A trend towards smaller patient populations is evident whilst tablet sizes and total dosing regimes have largely stayed flat.

- These findings only considered final API volume – so when considering other steps in the value chain, such as advanced intermediates, the overall volume requirement will be significantly higher.

- It is also evident there is a change in the manufacturing complexity of small molecule drugs which has shown an increasing trend towards more complex manufacturing requirements.

Volume evolution

The research trends showed a clear decline in the numbers of NCEs with volume ranges above 10 metric tons (MT) and below 10kg, while those reaching their peak volumes in the ranges 10kg-1MT and 1-10MT are stable or increasing. Of the 27 NCEs launched in 2014/2015, 12 are forecast to reach volumes of 1MT at their peak. The research shows that the spread of volumes is becoming narrower and that there is more clustering around the middle volume range now compared with 15 years ago (figure 3).

One conclusion that can be drawn from this is that the peak volume demand – at least within the US market – seems to be in the range of one to a few tens of metric tons of API. The numbers of drugs with a peak demand greater than 100MT has dropped, as have those below 10kg.

This data does not necessarily spell the end for the blockbuster era. Small molecule drugs that are in the region of 1-10MT volumes can still command in excess of $500M in sales. This is especially true for drugs used in oncology indications, where the pricing per unit is orders of magnitude higher than drugs used in more chronic indications such as hyperlipidemia and diabetes. Similarly, not all orphan drugs are low volumes, some are taken in high doses and consumed daily.
**Patient dose requirements**

There were no findings from the research that supported significant changes in the consumed amount of the APIs, nor in the size of the dosage. The majority of drugs are still in the 1-100g per patient per year range, although there was a slight increase in the number of lower dose NCEs below 1g per patient per year, according to the study (figure 4).

**Figure 4**

<table>
<thead>
<tr>
<th>Solid Dose Distribution Trend by API Unit Size</th>
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<tr>
<td>&lt;10 MG</td>
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<td>35%</td>
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<td>5%</td>
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Whilst the data does not yet show any real trends in a reduction in the total dosages consumed by patients, to receive a therapeutic effect the trend towards targeted medicines has not yet had time to manifest itself in our dataset as it is focused on commercial products.

Similarly, there has also been little change in tablet unit sizes: 10-50mg continues to be the most frequent dose size, although the 50-250mg size range is gradually increasing in popularity. This highlights one of the reasons for the continued prevalence of small molecule drugs is their ability to be taken orally - which is still a preferred method of administration from a patient compliance point of view.

**How is Cambrex set up to deal with this trend?**

**USA**

Cambrex’s facility in Charles City, Iowa currently employs approximately 375 people and is expected to grow over the next year to more than 400 employees.

This site has four full-scale cGMP plants, one cGMP pilot plant, three cGMP kilo labs, with one of those kilo labs capable of handling highly potent APIs with operator exposure limits (OELs) of less than 1µg/m³. The plants are multi-purpose, giving the flexibility to validate processes in multiple work centers to manage the lifecycle of the program, as well as offer the flexibility to adjust to the supply and demand needs of our customers.
Cambrex also has a high-potency development center at its Charles City facility, along with controlled substance manufacturing capacities, and the site is DEA Schedule II-V capable.

Cambrex maintains a strong quality track record with the FDA and DEA along with other official agencies. We host numerous customer audits throughout the year, along with unannounced internal audits in order to maintain our strong quality track record.

The site has an overall vessel capacity of 100,000 gallons across its work centers. Pharma 1, our small scale facility, has various glass, stainless steel and Hastelloy vessels from 500 to 2500 gallons, as well as a 1,200 gallon hydrogenator. Pharma 2 is a full-scale plant containing 2,000 and 4,000 gallon glass-lined reactors, Hastelloy filter dryers and a thin film evaporator.

Pharma 3 is our newest manufacturing plant and will be online mid-2016. It will contain two 2,000 glass-lined reactors, two 4,000 gallon glass-lined reactors, one 2,000 gallon Hastelloy reactor and one 4,000 gallon Hastelloy reactor, two Hastelloy filter dryers and a stainless steel fundabac filter. This facility will be able to handle compounds of an OEL of 1µg/m³ or higher allowing it to reach that borderline high-potency phase that some oncological programs would fall into.

Our pilot plant houses reactors up to 300 gallons and the site’s high-potency kilo lab and milling facilities. The cGMP kilo lab facility can handle 150 liter reactors and also OELs less than 1µg/m³. The milling facility contains cold mills, fixed mills and jet mills in sizes of two, four and eight inches.

To convert this capacity to batch sizes, the 2,000 and 4,000 gallon reactor trains typically produce a batch size of around 200 to 1,000kg per batch, allowing for campaigns up to 100MT of API or intermediates. From the pilot scale, the 100 gallon to 500 gallon reactors afford a 10 to 100kg batch size, which, depending on the chemistry, will allow campaigns from about 50kg to 1MT.

In 2017, Cambrex plans to expand its pilot plant capabilities by adding 300 gallon and 500 gallon reactors. We also have the shell of a new plant - nominally called Pharma 4 – built to offer a number of opportunities depending on future customer demands and needs. With the shell built, we are in a position of being able to install equipment and have the plant operational with only a six month lead time.

**How is Cambrex set up to deal with this trend?**

**Europe**

In Karlskoga, Sweden, we have a rich history in chemistry, dating back 120 years to Alfred Nobel himself in 1896. We produced our first APIs there in 1941 and were one of the first CMOs to enter the commercial manufacturing business.

Currently we have about 420 employees at Karlskoga, plus an additional 30 employees at our Tallinn, Estonia, laboratory. We have a wide range of production scales from kilo labs to up to large-scale cGMP commercial production units and have an excellent quality performance and regulatory track record.

The site in Sweden includes 4 cGMP pilot plants, 7 full scale production units and 14 production trains, supported by development and analytical laboratories and a cGMP kilo laboratory. The large-scale cGMP production plant, which we call F25, houses 16 reactors between 4-6m³, which are capable of handling large commercial volumes of multiple metric ton projects. This facility also has five reactors of 2.5m³, which would be classed as mid-scale.
In terms of investment at Karlskoga, we have had about a 50% increase in our CMO development capacity over the period 2014-16 and also expanded significantly in our analytical side, particularly in Tallinn.

These expansions included the addition of a 6m³ large-scale capacity and a further 12m³ of vessels to create a large cGMP multi-purpose production line. In addition, we have also noted the change in chemistry coming through the pipeline and thus invested in high potency capabilities by adding a Rosemund filter for high-potency production down to 1-10µg/m³ OEL. Finally, in terms of capability, we also added wet milling to our toolbox.

Conclusions
Taking all the factors from the research into account, we feel there are plenty of growth opportunities in the small molecule market. Key to this is for contract manufacturers to remain competitive and have the ability to be flexible enough to produce APIs in a range from kilograms to hundreds of metric tons to satisfy the wide variety of demand from customers. The trend towards a reduction in the average volume requirements for a small molecule highlighted in this research manifests itself as a big opportunity for CMOs, given their experience in handling multiple customer projects with varying volume requirements and chemistries. Unlike captive manufacturing at big pharma plants, CMOs are flexible and can adapt faster to the dynamic demands of the marketplace which is likely to include more complex molecules and chemistries. The trend for pharmaceutical companies to shutter their captive API facilities is poised to continue due to the evolving nature of the small molecule pipeline and their historic reliance on large (e.g. 100+MT) blockbuster products which required manufacturing at a different scale to what is required now.

The real balance is for CMOs to be able to offer a range of manufacturing options to their customers which can ultimately cover the entire lifecycle of the drug; from clinical development to product launch, then on to patent expiry and maturity. These manufacturing options should also be versatile to allow the possibility to work with customers both forwards and backwards along the supply chain if necessary; this could include becoming a supplier of key intermediates or starting materials if there is a regulatory or customer requirement to do so.