

Business *Awareness*

ISSUE 3 2009



Small Molecules are still Big Business for the Pharmaceutical Industry

Chemical synthesis for small molecule moieties is one of Lonza's key competencies within the area of custom manufacturing. Using the latest chemical processes, Lonza's Small Molecules business (LESM) offers its customers exclusive synthesis of chemical intermediates, active (and highly active/potent) pharmaceutical ingredients (APIs and HAPI/HPAPIs) and, more recently, antibody drug conjugates (ADCs) under full cGMP requirements for use in pharmaceutical products.

This chemical technology toolbox has emerged from the broad range of expertise that Lonza has gathered throughout its one-hundred-year history, strengthened with the opening of its fine chemicals complex (FCC) at its Visp (Switzerland) site in 1984. The FCC, now celebrating 25 years of operation, served to lay down the foundation for Lonza's custom manufacturing business in

which it thrives still today. The Visp site has constantly been expanded, most recently by addition of state-of-the-art production facilities for antibody drug conjugates and highly active/potent pharmaceutical ingredients. In addition, LESM operates other manufacturing sites in Riverside, PA (USA) and Nansha (China) which, when combined, offer the customer a formidable array of technologies and capacity to solve their manufacturing needs

| Life Science Ingredients | Custom Manufacturing: Exclusive Synthesis & Biopharmaceuticals | Bioscience |
|-----------------------------|---|-------------------|
| Nutrition Ingredients | Small Molecules | Cell Therapy |
| Microbial Control | Peptides | Rapid Testing |
| Performance Intermediates | Biochemicals | Media |
| | Mammalian Operations | Cell Discovery |
| | Biopharma R&D Services | Molecular Biology |
| | Microbial Operations | |
| | Pharma Sales and Marketing | |



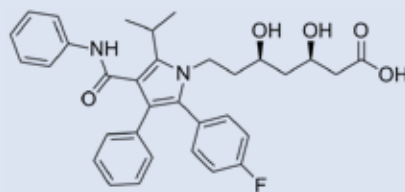
Eight of Ten Drugs are Small Molecules

Given the general trend towards biological drugs (often referred to as ‘large molecules’) and the investments Lonza has made in the area of biopharmaceuticals over the last decade, one might question whether small molecule manufacturing should remain a major focus to custom manufacturing organizations (CMOs).

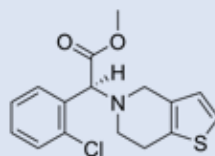
In this context, it is worth remembering that in 2007 the pharmaceutical market totalled USD 712 billion with 80% of this value due to chemical molecule drugs. If we look at the top ten drugs, we see that eight of them (Lipitor, Plavix, Nexium, Advair, Zyprexa, Risperdal, Seroquel and Singulair) are moieties based on small molecules.

Structures of the top 3 selling drugs:
Lipitor, Plavix and Nexium

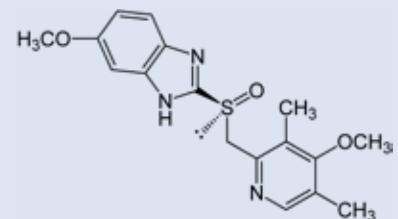
Lipitor (atorvastatin)



Plavix (clopidogrel)



Nexium (esomeprazole)

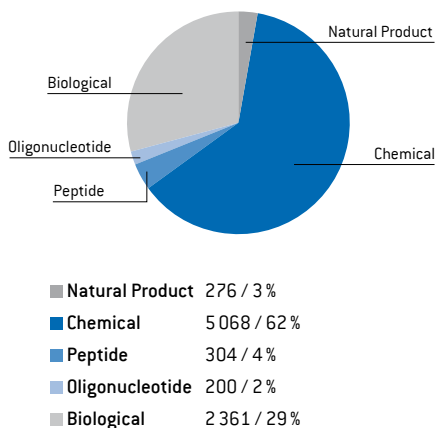


Even projecting forward a few years to 2012, USD 3 out of USD 4 from prescription sales will still be due to chemical entities. A glance at the pharmaceutical pipeline offers comfort further still, with 5 000 small-molecule candidates reported to be in clinical trials – the corresponding number for biologics is half this.

Small Molecules: Defined

The definition of “small molecule” is in no means unambiguous but in this context refers to a chemical molecule of low molecular weight, typically <500MW. The word “small” in this case is merely presented as a juxtaposition to “large” proteins and antibodies, whose molecular mass is usually 200-300 times greater. Often (but not always) these chemically-based drugs have structural similarities adhering to Lipinski’s ‘Rule of 5’ (empirically-derived observations and criteria that chemical entities need to satisfy to enable them to carry out their mechanism of action as drugs in the body.) From their roots in early medicine they have been at the forefront of the pharmaceutical industry since its conception in the 1900s. There are currently in excess of 2 000 small molecule drugs available on the market covering a seemingly limitless number of indications, ranging from common illnesses such as headaches and nausea to more aggressive diseases such as HIV and cancer. The majority of small molecule drugs are produced by synthetic means through mastery of organic chemistry – however some are also derived from natural products whilst many others can be obtained through biocatalytic and biosynthetic pathways (fermentation).”

Drugs in preclinical/clinical development split by molecule-type



New Chemical Technologies

Medicines are evolving and antibodies, proteins, peptides and oligonucleotides have all risen to challenge unmet needs as new pharmaceutical products. Chemical molecules are not staying still either. From the beginnings of the pharmaceutical industry with Aspirin in 1899 and penicillin in 1942, chemical molecules are evolving as fast as their biological brethren. In the past 100 years, we have witnessed quantum leaps in clinical efficacy, moving from ‘flat’ chemicals to chiral molecules (such as Lipitor and Zocor), to chemically synthesized peptides and oligonucleotides (such as Leuprorelin and Macugen), to highly potent and toxic APIs, and more recently, antibody drug conjugates. To keep up with demand, the pace of development of new manufacturing technologies has been equally swift – with developments in organic chemistry, asymmetric synthesis, new catalyst design, solid phase synthesis, biotransformations and recombinant and transgenic technology. It is through continual invest-

ment in new technologies and R&D that CMOs can remain competitive by ensuring secure delivery for tomorrow’s new breed of chemical entities.

Lonza has typified this by investing heavily in a suite of new technologies and leveraging different manufacturing sites across the world. A well-rounded custom manufacturer will embrace the current market excitement of biologics but continue to harness and invest in chemical synthesis in order to keep a broad, balanced portfolio of technologies. By optimizing synergies that exist between biotechnology and classical chemistry, Lonza provides alternative and innovative manufacturing pathways and is one of few top-tier CMOs to provide a complete service offering in small molecules, with a production capacity ranging from gramme to multi-tonne quantities. Small molecules are still big business for the pharmaceutical industry.





Lonza