DOI: 10.1002/anie.201103888

The Importance of Chemistry for the Future of the Pharma Industry**

Hanno Wild, Dirk Heimbach, and Christoph Huwe*

Hanno Wild, Senior Vice President – Global Drug Discovery, Bayer HealthCare – Wuppertal/Berlin

The pharmaceutical industry currently faces significant challenges, including a decreasing output of new medical entities, ever increasing regulatory requirements and risk perception in society, and more recently, reimbursement issues due to the desire of healthcare systems to reduce costs. The reasons for this development are manifold: Most of the low-hanging fruit have been picked, and targets and diseases that are now being addressed are increasingly complex and challenging; society tends to focus more on potential risks than on the advantages of novel medications; and to demonstrate net clinical benefit often requires large and expensive late-phase clinical studies. As a consequence, pharmaceutical companies have reacted by filling their portfolios through mergers, followed by cost-cutting measures, including substantial reduction of their research activities, which will likely result in a further decrease in output of these organizations.

True innovation will be the key to continued success

As a better alternative, many companies, including Bayer, believe that the current challenges can only be mastered by a strong focus on true innovation addressing unmet medical need, and thus providing medications with a real benefit for the patient. For this model to be successful, companies will have to strengthen their capabilities to innovate, to take risks, and to address novel and more difficult fields of research. At the same time, it will be required to generate a solid public understanding of the significant effort both in time (typically 12–14 years) and investment (two billion US dollars and more) required to deliver new drugs to patients, the existing unmet medical need, the public health risks associated with a lack of innovative drugs, and the potential for overall healthcare cost savings that innovative drugs can provide by reducing morbidity. True innovation will also be the only way forward considering the current development towards relative efficacy assessment of drugs and value-based pricing models being considered by some reimbursement systems.

Many diseases can still not be treated adequately

There still is a much higher unmet medical need than often perceived by the public. Today only about 300 of the estimated 6000 potential drug targets in the human genome are addressed by approved drugs. Although the impact of these drugs on public health is already remarkable, there remains a large number of diseases with limited or no treatment options, most prominently in oncology (e.g., malignant melanoma, ovarian, pancreatic, and small-cell lung cancer), but also in cardiovascular (e.g., stroke, heart failure, atrial fibrillation) and neurodegenerative diseases (e.g., Alzheimer's, Parkinson's, multiple sclerosis), women's healthcare (e.g., endometriosis, myoma), and, on the rise again, infectious diseases (e.g., multiresistant bacteria, new flu viruses).

In order to address these challenges, pharmaceutical companies need powerful R&D organizations characterized by outstanding scientists, room for creativity, and operational excellence in all areas from drug discovery and development to the business units. Of course, no research organization is able to solve all of the current scientific issues alone, so a strong network in all locations globally with proven or growing innovation potential, new types of collaborations between industry, national and nongovernmental research organizations, scientific societies, and academia, including open innovation concepts, are essential means to broaden the accessible scientific base. In addition to cutting-edge basic science, academia can and should contribute a healthy openness to collaborations with industry when it comes to applied science, as quite common in the United States and improving in Europe.

Chemistry has always had a crucial role in drug discovery

Organic chemistry has been a driving force for drug discovery since its very beginning. After the isolation and characterization of the pure chemical ingredients of natural medicines (e.g., morphine, 1804), the first synthetic drugs were developed (e.g., nitroglycerine, 1844), and soon thereafter the first systematic drug-finding efforts led to significantly enhanced treatment options (e.g., Aspirin, 1897; Salvarsan, 1909; plasmoquine, 1926). Since then, organic chemistry, through medicinal chemistry as its specialization for the discovery of small-molecule drugs, has had a growing impact on an ever-increasing number of disease areas.

However, with the impressive therapeutic success of protein drugs (e.g.,

[*] Prof. Dr. H. Wild, Dr. D. Heimbach, Dr. C. Huwe
Bayer Healthcare AG, Global Drug Discovery, Candidate Generation and Exploration
42096 Wuppertal (Germany)
E-mail: hanno.wild@bayer.com

[**] Some related considerations have been previously published online: H. Wild, D. Heimbach, http://dx.doi.org/10.1002/chemv.201000055.

Enbrel, Epogen, Betaferon/Betaseron, Kogenate) and therapeutic antibodies (e.g., Remicade, Humira, Avastin) came the idea that small molecules would eventually be replaced by biological approaches. This has sometimes led to the view that medicinal chemistry should now focus on the modification of larger systems and chemical biology. While this approach certainly makes sense in order to further broaden the impact of chemistry on drug discovery—antibody–drug conjugates are an excellent example—we believe that this notion is misleading.

Small molecules will maintain their significant relevance

For the benefit of the patient, the pharmaceutical industry needs to utilize all available therapeutic options, including biologicals and novel concepts that are still in their infancy, for example, treatments based on small interfering RNA (siRNA). However, we are convinced that small molecules, and therefore medicinal and organic chemistry, will continue to play a very important role in drug discovery.

In 2009 about 75% of blockbuster drugs with annual sales over one billion US dollars and 70% of the new medical entities launched in 2010 were small molecules. Significant therapeutic progress has been made during the last years by addressing novel target classes with small molecule modulators, for example, HMG-CoA reductase in lipid disorders (e.g., Lipitor), kinases in oncology (e.g., Gleevec, Nexavar), HIV protease in antiviral therapies (e.g., Viracept, Aptivus), and proteases like thrombin and factor Xa in thrombotic disorders (e.g., Pradaxa, Xarelto). More recently, progress has also been made in the area of protein–protein interactions, which are often considered as difficult targets for small molecules, by discovering compounds that block critical binding sites on the contact surfaces (e.g., inhibition of MDM2/p53 interaction by nutlins).

Moreover, small molecules are able to interact with both extra- and intracellular targets. Acting on molecular targets inside the cell, they offer a vast repertoire of therapeutic options not readily accessible for other drug entities. Small molecules can be designed to pass through the blood–brain barrier or not, and precise adjustment of the duration of drug action as well as of inhibitory or stimulatory effect is achievable. Small molecules can also be specifically designed for intravenous administration often needed for acute treatments with a faster onset of drug action and possibly rapid elimination of the drug upon cessation of treatment. Finally, oral administration is also possible, which is generally safer and more convenient for many chronic applications and helps to reduce treatment costs by reducing the number of necessary doctor visits. In addition, the cost of goods of small molecules is typically much lower than for biologicals, and their accessibility for manufacturing and simpler supply chains offer additional advantages, particularly in emerging markets or developing countries.

The central role of chemistry creates broad opportunities

The chemical structure of a compound is responsible for virtually all of the parameters that determine the feasibility of a substance to eventually become a drug, including potency, selectivity, absorption, distribution, metabolism, excretion, toxicity, feasibility of synthesis, and patentability.

As a consequence, many research areas in chemistry need to contribute to the toolbox medicinal chemists require for the optimization of chemical compounds for the use as drugs in humans along the parameters mentioned above. Academic research has to contribute by advancing organic chemistry in order to broaden the accessible chemical space and to enable access to compounds with optimal physicochemical and pharmacokinetic properties, by developing new synthetic methodologies to introduce substituents into virtually all positions of a molecule, and by improving yield, selectivity, scalability, and economics of chemical transformations.

In addition, as our current understanding of the challenges of the multiparameter optimization processes of medicinal chemistry programs is far from complete, theoretical chemistry, in collaboration with structural biology, should continue to refine concepts in de novo design and molecular modeling in order to further improve the utility of computational chemistry predictions.

The opportunities that develop in these research areas are huge, but we need a strong interaction between academic and industrial research, where each side is open to collaborate and learn from the other, but that also focuses on those research fields where the individual partners can provide real excellence.

The impact of chemistry goes beyond small molecule drugs

So far, we have only discussed the role of chemistry in the development of small-molecule drugs. We don't want to conclude without mentioning that chemistry can contribute much more in today's and future pharmaceutical research. Tool compounds—provided they have the right activity, selectivity, and pharmacokinetic profile—can be used to elucidate mechanisms and to support chemical biology. Biological macromolecules can be synthesized or manipulated by chemical means in order optimize them to drugs or to investigate biological systems. In addition, chemistry plays an important role in the field of diagnostics and also contributes to the development of biomarkers, which will play a central role in the emerging area of personalized medicine.

In conclusion, it should be clear that there is no future for pharma R&D without chemistry, and that this vibrant field with bright prospects offers many opportunities for scientists interested in excellent research. Finally, due to the central role of medicinal chemistry in modern drug discovery, chemists, in close collaboration with colleagues from biochemistry, pharmacology, pharmacokinetics, and toxicology, are key players in managing drug-discovery projects in the pharmaceutical industry, which provides interesting career opportunities outside of pure research.