The discovery doldrums

NCEs are coming slowly; Jürgen Drews explains why.

"Biology and pharmacology do not function within the constraints of disease phenomenology," says Jürgen Drews, managing partner at Bear Stearns Health Innoventures Management, LLC, and former president of global R&D at Hoffman-La Roche, trying to explain why Big Pharma has fallen behind in the job of producing the new chemical entities (NCEs) needed to keep the industry strong. Drews offered this wisdom as part of his plenary lecture at the Lab Automation 2004 conference in San Jose in February.

As Drews explains it, recent technological developments and changes in philosophy in drug discovery have created a gap between the expected number of NCEs that should be produced by current drug discovery initiatives and the actual number being approved by regulatory agencies such as the FDA. For example, Drews points out that if you discounted protein-based products and off-patent generics or derivatives of existing drugs, less than half of the NCEs approved by the FDA in 2002 were actually new. In short, he concludes, the pharmaceutical industry has not been as productive as it should be given its vast outlays of money and effort, and this shortfall has led, to some extent, to the recent consolidation wave that has swept the industry.

Shifting focus

Drews explains that in part, this problem has been the result of endeavors like the Human Genome Project and bioinformatics, which have moved the pharmaceutical industry from a chemical focus to an informational focus in medicine.

"The drug research paradigm has moved from a compound looking for an effect to targets looking for a compound," Drews says. "And this led to a dramatic change in screening, from approximately 200,000 samples per year to 10 million."

But this switch in philosophy hasn't led to increased productivity. "It was a total flop," he comments. "It didn't do anything."

A major bottleneck has been that the rate of newly validated targets remains low, Drews says, with as few as four or five per year per company being considered a good benchmark. Likewise, he believes that the industry must move from diversity-oriented chemistry—as typified by combichem—to target-oriented chemistry.

Jürgen Drews

"Although there are 10^{62}–10^{63} druglike molecules—not following Lipinski's rules, but using reasonable constraints—there are only about 10^{4} possible targets," says Drews. "Thus, we need to refine our view of a lead."

As proof, he offers the example of the privileged-structure concept, in which simple molecular scaffolds can bind several types of target structures. This model suggests that the number of compounds needed to address most targets might be much smaller than initially believed, and that success in the drug discovery arena will lie in taking a "master key" or "in cerebro" approach.

Drews's clues

All, of course, is not doom and gloom, and Drews offers some suggestions about how the pharmaceutical industry might pull itself out of the NCE doldrums. His first suggestion gets back to the idea that drugs act on molecular targets, not diseases. Big Pharma wants to focus on specific medical areas, whether cancer, diabetes, or hypertension, Drews says, but each of these disease states shares numerous members of target families, such as G-protein coupled receptors (GPCRs), kinases, and cyclins. Thus, he says companies should instead focus their attention on these targets rather than on the disease states and become specialists in the drugs that will bind specific targets. This philosophy is more traditionally held by small biotech companies, if only because they lack the resources—financial and technical—for widespread screening.

Biotech is also pulling the market forward, according to Drews, because it has accounted for about a third of the new

Drug R&D has shifted from a chemical to informational focus

Chemical	Informational
Biological functions and structures can be described in chemical terms.	All biological functions and structures are manifestations of nucleic acid information.
Disease can be correlated with biochemical imbalances.	Disease results from deficient, superfluous, or redundant information.
Chemical correlates of abnormal biological function are of diagnostic and prognostic interest.	There are diagnostics-relevant relationships between the information content of cells and diseases.
Diseases can be treated with chemical therapeutics.	Diseases can be cured by substituting for missing or erroneous information.

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molecular entities produced over the past several years. Biotherapeutics, however, are only a means to an end. Rather than simply using biopharmaceuticals as the final product, Drews suggests that drug developers focus on developing chemical mimetics of these biologics with the goal of improving pharmacokinetic and pharmacodynamic profiles. Deficiencies in these two profiles represent the reason that almost 60% of NCEs fail to become marketable drugs. The development of chemical counterparts to biotherapeutics will also facilitate and simplify production.

Finally, Drews strongly advocates the goal of individualized medicine and suggests that pharmacogenomics is key. He believes, however, that the focus of researchers should remain on the development of broader-based haplotype markers—the HapMap—as genetic bar codes, rather than on identifying single nucleotide polymorphisms (SNPs). "The SNP approach was much too general to make any sense," he says, whereas haplotypes are much less unwieldy and should allow clinicians and researchers to group patients into collections of responders, nonresponders, and those who suffer from adverse reactions to a specific treatment.

"Drug research, as it stands today, is still a child of organic chemistry," Drews says. The future success of drug discovery, he believes, relies on researchers maximizing their efficiency by working on several parameters at once while maintaining an understanding that activity in an assay does not necessarily mean that a compound will be a drug.

—RANDALL C. WILLIS ■

About the subject

Jürgen Drews, M.D., has 40 years of experience in clinical and academic medicine and the pharmaceutical industry, including 3 years focused on venture capital. He joined Bear Stearns from IBMP, a $70 million biotech venture fund, where he was co-founder and chairman of the board.

Drews is the author of the 1999 book *In Quest of Tomorrow's Medicines.* He serves on the board of several leading biotech companies and is past president of the Brussels-based Senior Advisory Group on Biotechnology (later named EuropaBio). Drews is a professor of internal medicine at the University of Heidelberg, Germany, and a professor of molecular genetics at the University of Medicine and Dentistry, New Brunswick, NJ. He received his M.D. degree from the Free University of Berlin and did postdoctoral work at the University of Frankfurt and Yale University.

(Excerpted from *www.healthinnovation.com*)