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Restructurally sound

Facing dwindling product pipelines and looming patent cliffs, nearly all of the world's major drugmakers have recently overhauled their research and development activities. **Brendan Borrell** asks what difference these efforts have made.

In November 2004, Sanofi-Aventis thought it had the next blockbuster weight-loss drug. At the time, several of the French drugmaker's biggest hits, including the allergy pill Allegra and the insomnia medication Ambien, were about to lose patent protection, and the pharmaceutical company—the world's third largest at the time—needed a winner.

At the American Heart Association's annual meeting in New Orleans that year, researchers from New York's Columbia University Medical Center presented phase 3 clinical trial results on Sanofi's Acomplia (rimonabant), a drug that shuts off cannabinoid receptors in the brain to suppress appetite. The two-year trial involving more than 3,000 obese and overweight people across North America revealed that subjects taking Acomplia shed around 20 pounds on average and showed improvements in their levels of circulating triglycerides and 'good' cholesterol. The American Heart Association named it one of the top ten advances of the year. Soon after, Sanofi predicted annual sales of $3 billion—about one tenth of the company's global income.

Acomplia landed on pharmacy shelves in Europe and parts of Latin America in the summer of 2006, but Sanofi remained tight lipped about the new drug's timetable for entry into the US market, where the population's waist size is rivaled only by its medical spending. That February, the US Food and Drug Administration (FDA) had sent a letter to Sanofi saying that Acomplia was 'approvable', but the agency stopped short of giving the drug the full go-ahead, and for months neither Sanofi nor FDA officials revealed what the hang-up was. Then, stories started to trickle out about possible side effects. Two people on the drug committed suicide, and another man tried to strangle his daughter. Others described delusions, seizures and suicidal thoughts. In June 2007, the FDA rejected the drug, and, in 2008, the European Medicines Agency recommended pulling it from pharmacies.

The Acomplia failure became the company's soul-searching moment. "We realized about two years ago that the old ways of doing drug discovery were not working anymore," says Marc Bonnefoi, Sanofi's deputy head of US research and development (R&D). Sanofi finally took a hard look at the potential risks and benefits of drugs in their pipeline and began pondering strategies to restructure their R&D organization.

Sanofi is hardly alone in its struggles. The next two years will bring a peak in the number of leading drugs going off patent, including Pfizer's Lipitor, Eli Lilly's Zyprexa, Merck's Singulair and AstraZeneca's Seroquel. In the decade-long lead-up to this milestone, drugmakers have engaged in a record number of megamergers: Merck picked up Schering-Plough, Pfizer swallowed Wyeth, Roche acquired Genentech and, of course, Sanofi-Synthélabo took over Aventis in 2004 and then Genzyme earlier this year. Although these moves cut inefficiencies and pooled development risks, they did little to revitalize these companies' flagging drug pipelines—depleted from too many botched attempts at blockbusters and 'me too' drugs.

Sales and marketing teams had become entrenched in drug development so early in the process that drug discovery had shifted from a scientific process into a commercial one, with chemists, biologists and doctors performing their duties like cogs in a machine. At the time Sanofi was pursuing Acomplia, for example, more than ten other obesity drugs were also in clinical trials.

"The industry has had a lot of money over the years, and when things went bad in terms of efficiency they just pumped more money into it," says Kenneth Kaitin, director of the Tufts Center for the Study of Drug Development in Boston. "That doesn't work any more, and investors are saying they don't have faith in the industry's ability to bring products to market."

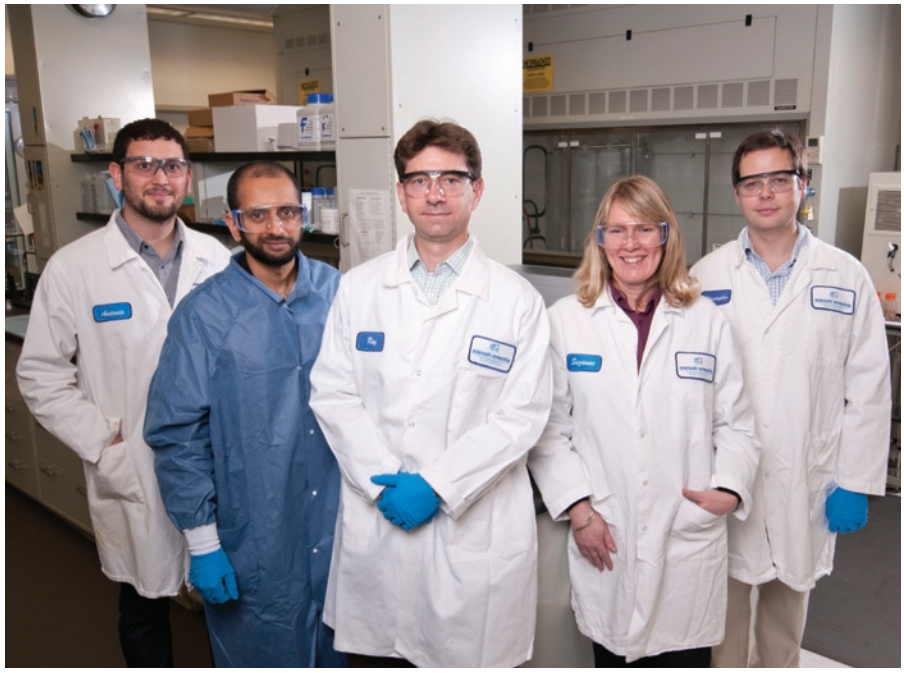
The challenge, notes Kaitin, is to maintain the spark of creativity that discovery science demands while ensuring that these findings can translate to advances and profits in the medical world. To foster that spirit of inventiveness, ten years ago GlaxoSmithKline (GSK) implemented a team approach to drug discovery by creating 'centers for excellence' focused on specific therapeutic areas, including psychiatry, cancer, metabolism and respiratory diseases. AstraZeneca, Pfizer, Novartis and Roche copied the teamwork blueprint, launching their own semiautonomous, biotech-like entities. Meanwhile, Eli Lilly took another tack, outsourcing drug development to a wholly owned subsidiary called the Chorus Group under the thinking that this offshoot could do things faster and cheaper than its parent company. At the same time, Bristol-Myers Squibb has been acquiring promising biotechs as part of its 'string of pearls' strategy, whereas Merck has scaled back to focus on seven therapeutic areas at 16 multidisciplinary facilities.

Sanofi remained one of the holdouts clinging to the traditional R&D model. Not anymore.

Strategic planning

By the end of 2008, Sanofi's shares had plummeted by more than 30% from a high in early 2006. In October, the company brought in a new CEO, a German-Canadian named Chris Viehbacher who had previously led GSK's North American division. Viehbacher didn't waste any time. In February 2009, he brought in former US National Institutes of Health director Elias Zerhouni as a scientific advisor; earlier this year, Zerhouni became global head of R&D.

Under Viehbacher's leadership, the company created an R&D 'investment committee' populated with scientists, sales managers and members of the insurance community to put the company's bloated portfolio through a stress test. The company reported 113 compounds in February 2008, but by the time Viehbacher was done that number was down to 55. Viehbacher promised not to lay off any researchers. Instead, he set out to reinvent the way Sanofi did research.



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Ray of hope: Ray Jupp (center) and members of the fibrosis and wound repair unit.

For starters, Viehbacher created five 'therapeutic strategy units' (TSUs): slender, 100- to 200-person entrepreneurial structures spread across Sanofi's R&D sites in the US, Europe and Asia. Rather than focusing on traditional biomedical subject areas, such as cardiovascular health or diseases of the central nervous system, the TSUs were designed strategically with interdisciplinary teams in mind. Clinical workers were brought in at the earliest stages of drug discovery, and teams that had traditionally pursued small molecules opened themselves up to alternative approaches, such as RNAi. The company also enacted a special 'evidence and value development team' to work with the TSUs and business units to smooth the transition from early R&D to product development.

Three of the TSUs are aimed at major disease areas where there's a considerable unmet medical need: immunoinflammatory disorders, infectious diseases and fibrosis and wound repair. The other two TSUs focus on two growing markets: the elderly (or, more specifically, the physiology of aging) and people in the Asia-Pacific region. Although commercial potential was built into the design of the units, researchers were also granted greater control over the choice of projects to pursue. The job of the TSUs, which now make up 30% of the company's R&D operation, is to shepherd projects from discovery through the clinical trials by working in concert with members of Sanofi's larger 'scientific core platform'.

Just over a year after the February 2010 transition, Ray Jupp, vice president of the fibrosis and wound repair unit, says he is already seeing results. He points to success in treating fibroproliferative disorders, the excess growth of connective tissue found in nearly half of all individuals at the end stages of diseases, including some 2,000 diseases that affect the kidneys. "We can't go into 2,000 diseases at once," Jupp says, "but we'll identify a disease in which we can really show an effect and get a reasonable number of patients in a reasonable time frame."

On a recent afternoon at Sanofi's US headquarters in Bridgewater, New Jersey, medicinal chemist Joyce Yang shows off a glass beaker containing a gallon of brownish-green sludge—plant extracts being tested for their ability to halt myofibroblast proliferation, collagen deposition and other variables relevant to fibroproliferation. The fibrosis group's botanical efforts kicked off last year after the unit's first two-hour brainstorming workshop following the R&D transformation. One researcher suggested that the team work within the FDA's guidelines on botanical extracts, which provides a shorter route to approval of new drugs that use extracts from plants that have been recognized as safe. "This was a grassroots effort," Jupp says.

Other TSUs are adopting research strategies

tailored to their own needs. For instance, the immunoinflammatory unit is taking a gateway approach by focusing on psoriasis, with the hope that insights gleaned from the chronic skin disease can be applied to other autoimmune disorders more generally. "It's a way of testing a concept and moving onto more complex systems," says Mike Tocci, vice president of immunology research.

Jupp also argues that the independent and flexible nature of the TSUs has directly encouraged closer collaborations with academic institutions and small biotechs. In February, for instance, his group entered into a research and licensing agreement with Sunnybrook Health Science Centre in Toronto for vasculotide, a compound that could be used to treat diabetic foot ulcers. Sanofi now claims to be licensing more compounds from the outside than it ever did in the past, with approximately half of the TSUs' drug discovery conducted in collaboration with external partners.

But Damien Conover, a pharmaceutical industry analyst who covers Sanofi for Chicago-based Morningstar, isn't convinced that the restructuring has paid off. "Their pipeline is neither better nor worse—just different," he says. "I'm skeptical that these division structures have value. They may help in reducing cost, but increasing productivity?"

Model building

Most analysts agree that it's still too early to tell whether smaller units like those at Sanofi will translate to more successes in the long and twisty drug pipeline—particularly as the record from other companies has been mixed. According to the Biotechnology Industry Organization, a lobby group based in Washington, DC, just one in ten drugs made it from clinical trials to FDA approval between 2003 and 2010, the main period of the industry's R&D reorganization; in the past, that rate was closer to one in five.

"These are broad-based, structural issues, and until we have a better way of managing and succeeding at R&D, it's hard to know whether the industry is digging out of the fold," says Viren Mehta, a founding member of the biopharmaceutical consultancy Mehta Partners in New York.

Still, drugmakers continue to throw their support behind these entrepreneurial models. Four years ago, for example, GSK, which was first out of the restructuring gate with its Centres of Excellence in Drug Discovery in 2001, started breaking up its seven centers into what are now 38 'drug performance units'. Even though some critics point to the London-based drugmaker's ongoing restructuring as a sign of failure, GSK's chairman of R&D Moncef Slaoui says that it was just the next step in an evolution that has given scientific talents a chance to express their vision and take ownership of their projects. "Frankly, what we've been doing since 2001 is a continuum of the same philosophy," he says.

Eli Lilly, meanwhile, claims that since creating its Chorus subsidiary in 2002 the autonomous research laboratory has been able to reach decisions on molecules 12 months earlier and at half the cost than the traditional industry model. In fact, the Indianapolis, Indiana–based company is so confident in its R&D pilot project that earlier this year it established new Chorus spin-offs in the US, Europe and India.

Similarly, many others—including AstraZeneca, Bristol-Myers Squibb and Merck, just to name a few—are less interested in redefining the way scientists work inside the company than in trying to externalize the earliest and most risky phases of the drug discovery process. In fact, even the world's largest drugmaker, Pfizer, is considering this approach. In March, newly minted CEO Ian Read hinted at plans to spin off or sell the company's nonpharmaceutical divisions, including nutritionals and animal health.

Cheryl Barton, a biochemist who runs the consultancy PharmaVision in West Sussex, UK, says this outsourcing represents a sea change from the old way of doing things. "When I worked at Merck years ago, it was one of those companies that didn't outsource anything at all," she says. "It took great pride in being able to do everything internally, and it was frowned upon if you had to go outside to do anything at all."

Trying to keep track of all the changes afoot in the industry is daunting. And, as yet, no single strategy has emerged as a clear winner. So, in the meantime, companies continue to pursue the approach that best seems to fit their business models. "No one has found a solution to the patent cliff," notes Sanofi's Bonnefoi. "No one has written the book. We need to write it ourselves."

Making the team: Pharma's team-based R&D units and collaborative programs.

GlaxoSmithKline	Drug performance units
Novartis	Novartis Institutes for Biomedical Research
Roche	Disease biology area leadership teams
Sanofi-Aventis	Therapeutic strategy units
Pfizer	Global Centers for Therapeutic Innovation
Eli Lilly	Chorus Group's Fully Integrated Pharmaceutical Network
Johnson & Johnson	Five 'therapeutic areas'[a]
Merck	Therapeutic franchises and functional units

[a]As yet unnamed.

Own it: Moncef Slaoui advocates allowing scientists to follow an entrepreneurial model.

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