

## Will CROs Find Opportunity in a Reinvigorated European R&D Sector?

*The EU must harness market forces that reward innovation and competitiveness to combat its current R&D drain*

Europe's bureaucrats are launching a new effort to reverse one of the European economy's most disturbing trends: the loss of its pharmaceutical R&D sector. The European Union's (EU) success with its new campaign is critical to the long-term success of the European CRO business.

Responding to the widely perceived decline of Europe's role in R&D, the director of the Council of the European Union commissioned a study about pharmaceutical competitiveness — "Global Competitiveness in Pharmaceuticals: A European Perspective" — commonly referred to as the Pammolli Report. The results detailed in the report indicated that to solve the problem, the EU must harness the market forces that reward innovation and maintain competitiveness. The report stated that "Europe is lagging behind in its ability to generate, organize, and sustain innovation processes that are increasingly expensive and organizationally complex."

The EU responded to the Pammolli Report's assessment with a set of comprehensive recommendations designed to reform the European drug sector. The guidelines, called the *G10 Report on*

*Medicines*, are now at the center of debate and discussion in Europe (See "Guidelines from the EU's *G10 Report*" sidebar). The biotechnology sector is being addressed by separate initiatives.

Although it promotes its vision of reform, the EU is facing resistance both from member countries and from the pharmaceutical industry. Member countries do not want to give up their authority to set drug prices, and the EU's pharmaceutical industry is fighting the government's emphasis on generic drugs and its efforts to centralize all new drug approvals in the European Agency for the Evaluation of Medical Products (EMEA, [www.emea.eu.int](http://www.emea.eu.int)). The result is a fragmented market in which drug-to-market progress is slow and costly with no immediate solution in sight.

### Fighting a Long-Term Trend

Europe has been losing its pharmaceutical R&D base for some time. The recent Novartis International ([www.novartis.com](http://www.novartis.com)) decision to move its flagship R&D operation from corporate headquarters in Basel, Switzerland, to a facility in Cambridge, MA, is the latest high-profile example of Europe's pharmaceutical "brain drain." European-based companies AstraZeneca ([www.astrazeneca.com](http://www.astrazeneca.com)) and GlaxoSmithKline ([www.gsk.com](http://www.gsk.com)) have their principal R&D operations in U.S. cities, and CRO executives have noted that R&D decision making is generally centered in the United States.

The data don't paint a pretty picture for European pharmaceutical R&D. According

to the European Federation of Pharmaceutical Industries and Associations (EFPIA, [www.efpia.org](http://www.efpia.org)), U.S. pharma R&D investment rose fivefold between 1990 and 2001, and European investment grew only 2.4 times.

The Pharmaceutical Research and Manufacturers of America (PhRMA, [www.phrma.org](http://www.phrma.org)), whose members include large European-headquartered sponsors such as Aventis ([www.aventis.com](http://www.aventis.com)), AstraZeneca, and GlaxoSmithKline, recently reported in its *Pharmaceutical Industry Profiles 2002* that nearly 80% of member R&D dollars was spent in the United States in 2001. Only 10% was spent in Switzerland and the countries belonging to the EU.

European spending on biopharmaceutical R&D is also much less than its U.S. counterpart, according to consulting firm Ernst & Young (E&Y, [www.ey.com](http://www.ey.com)). In its report, *Beyond Borders: The Global Biotechnology Report 2002*, E&Y reported that European biotech R&D spending is only half that of the U.S. biotech industry and that securing funding for biotech ventures is much more difficult in the European market.

Part of the problem is that the United States offers more favorable market conditions for selling new drugs. According to EFPIA, 62% of the sales of new medicines marketed since 1997 has occurred in the U.S. market, compared with 21% in the European market. New drug sales in the European market are impeded by the prevalence of *parallel trade* — the practice of buying a drug in one country and selling

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it at a profit in another country where the price of the drug is higher. Parallel trade is a direct result of various drug price-control schemes among European countries, and EFPIA estimated that the practice cost drug companies 3.5 billion in 2000 alone.

Attracting talent has been another big factor in the shift of R&D across the Atlantic. "If you want to be among the best companies in the world," said Novartis spokesman Mark Hill, "you must have the best researchers. There is much more high-quality talent in the United States because there is more investment — 50 times as much — put into basic research, which is what attracts the talent."

### The UK Tries its Own Solution

One member state that is not waiting for EU R&D reform is the United Kingdom (UK). Already the most hospitable locale for pharmaceutical R&D in Europe, the UK is offering large British and foreign companies operating in the region an

additional 25% deduction from their taxable income for current spending on qualifying R&D. The R&D tax credit, which applies to all industries, became effective 1 April 2002 and is expected to cost £400 million annually.

Observers say the new tax credit, along with a similar measure for small- and medium-sized companies that was enacted two years ago, will increase the country's

attractiveness to foreign pharma companies. However the effectiveness of the tax measures in expanding R&D and its infrastructure cannot be measured right away because of lags in reporting and accounting.

To promote links between businesses and other institutions, companies are allowed to claim deductions for funds provided to hospitals, universities, research organizations, and other nonprofit entities.

### Guidelines from the EU's G10 Report on Medicines

The *G10 Report on Medicines* is meant to be the EU's blueprint for reviving its pharmaceutical R&D sector. The report calls for efforts to

- speed innovative drugs to market after authorization
- reduce market fragmentation
- increase the transparency of market authority among states
- enlarge the supply of generic drugs while maintaining intellectual property protection of innovative drugs

- increase the movement of drugs from prescription to nonprescription status
- link research centers to forge virtual institutes of health
- coordinate clinical trials on a European scale
- increase the flow of information about medicines to patients.

The full report is available at <http://pharmacos.eudra.org/F3/g10/docs/G10-Medicines.pdf>.

Tax credits for work based in the UK also aim to encourage foreign companies to relocate their facilities.

The tax credit is seen as both a spur and a reward to the pharmaceutical industry, which already conducts nearly 40% of the UK's industrial research. The pharma industry also has a close relationship with government agencies and committees with which it partners to expand access, fund scientific research, increase National Health Service spending, and ensure the humane treatment of animals in clinical trials.

The UK's pharmaceutical industry, although not on a par with the United States, is considered the best and the most intensive R&D in Europe, prompting global companies to locate research facilities there. UK government reports state that 25% of the tax credit will go to pharmaceutical companies: 17% to UK-based pharmaceutical companies and 8% to the overseas subsidiaries of foreign pharmaceutical companies such as Merck ([www.merck.com](http://www.merck.com)) and Pfizer ([www.pfizer.com](http://www.pfizer.com)).

Britain's largest pharmaceutical association is solidly behind the tax credit, believing that the industry has worked hard for a credit and that global business conditions require it. "The UK industry invests a large sum of money — more than £8 million per day — which is the highest R&D investment in Europe," says Richard Ley, spokesman for the Association of the British Pharmaceutical Industry ([www.abpi.org.uk](http://www.abpi.org.uk)). "This [investment amount] is a long way behind the United States, and it is not increasing by the same proportion. We believe the tax credit will be a good contribution for large and small pharma; it will provide an incentive for continued investment."

### **A Temporary or Permanent Shift?**

Not all observers see the migration of R&D spending to the United States as a public policy problem. For Wolfgang Greb, CEO of German CRO FOCUS Clinical Drug Development GmbH ([www.focus-cdd.de](http://www.focus-cdd.de)) in Düsseldorf, Germany, the shift of pharma R&D to the United States is nothing more than a temporary geographic adjustment in the global pharmaceutical industry.

Greb states that the companies that have been relocating their R&D sites to the United States should be doing so because of their size and their need for a global presence. But the companies that have remained in Europe should stay because their interests are invested more heavily there. "But even now some companies are finding that it is not all heaven that they will experience in the United States. Although they are first attracted [to the United States] by the simplicity of conducting studies, the high-priced market, and a single medical standard, some are beginning to find that cost-cutting is an issue and that generics will increase in the United States, too," Greb said. He predicts that the number of R&D sites will once more shift in Europe's favor, but he also stated that this could change in two years when 250–400 million people from Poland and Czechoslovakia join the EU. "This [event] will be a substantial enlargement that will seriously increase costs [in Europe], which may shift the balance again," Greb said.

Other companies watch with greater concern as the industry votes with its feet on the EU's performance and probably will continue to do so. Pfizer's Peter Farrow says his company places innovation high on the list of important market qualities. "We generally view the United States as an area that more readily rewards the efforts of innovation,

and it is also the largest pharma market in the world," he said. "These issues rank high when making decisions about where to place research. In addition, the high standards of the American scientific base and the ease with which we can build good collaborations with

universities are critical to research productivity."

Will the current EU process fix the problem? "The G10 people are taking a long time to deliver real value," said Farrow.

"Without in-depth follow-up work and a whole new approach to industry-government collaboration, they won't be able to fix the competitiveness of European R&D." **BPI**

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## Jim Miller's Outlook

Most CROs have reported strong financial results during the past 18 months, and a big reason for these results is the demand for preclinical research and testing services.

In the most recent quarter, for instance, **Covance** ([www.covance.com](http://www.covance.com)) reported 16% year-over-year growth in its Early Development Services unit, which includes preclinical testing. **Charles River Laboratories, Inc.** ([www.criver.com](http://www.criver.com)), reported 16% growth in its services business, which is focused on preclinical and biosafety testing. **Inveresk Research Group** ([www.inveresk.com](http://www.inveresk.com)), the newest public CRO, reported that preclinical revenues were up 34% for the quarter, and **Bioanalytical Systems, Inc.** ([www.bioanalytical.com](http://www.bioanalytical.com)), saw testing revenues jump 11%.

Growth in demand is outpacing the CROs' ability to add new capacity. Covance officials say that six rooms in its Madison facility expansion have been presold, and Inveresk's management indicated that much of the capacity being added to its Montreal, Canada, and Edinburgh, Scotland, facilities has already been sold. Bioanalytical Systems executives said that new facilities now under construction would be filled soon after completion.

Inveresk officials estimated that annual industry spending on preclinical toxicology is about \$4 billion, with 20–25% of that total outsourced. The company said demand for specialty toxicology services is particularly strong, including inhalation and infusion toxicology. Covance officials noted that many major pharmaceutical companies are outsourcing all of their studies lasting 90 or more days. Demand from biopharmaceutical companies, many of which lack their own testing facilities, has also been a factor. For example, 323 commercial investigational new drug applications (INDAs) were filed with CBER ([www.fda.gov/cber](http://www.fda.gov/cber)) for biologics candidates in 2001, an increase from the 239 filings in 1999. All of those IND filings must be supported with preclinical testing results.

Another benefit for CROs in the preclinical testing business is that it seems to be immune to the effects of industry mergers and acquisitions. CRO executives' experience during the late 1990s demonstrates that preclinical studies seldom get cancelled following mergers.

### What Shortage?

Despite dire warnings of biomanufacturing capacity shortages, biopharmaceutical companies do not seem to be experiencing major project delays. Manufacturing and supply-chain managers in the industry report that although they may not

always get the scheduling they would prefer, they are able to get clinical projects done without too much delay. Industry experts are saying that delays that do exist can be used by sponsors to perform additional process development work, which usually yields more clinical trial material for their clinical testing programs. Biopharmaceutical companies, especially smaller ones, often tend to skimp on early process development efforts to save money and to get to the clinic faster, but the poor manufacturing processes that result can have the opposite effect.

The biomanufacturing industry continues to roll out plans for new capacity, albeit at a cautious pace. In a recent announcement, **Cambrex Bio Science** ([www.cambrex.com](http://www.cambrex.com)) revealed that it will undertake a \$26 million expansion of its biomanufacturing capacity at its Baltimore and Hopkinton, MA, locations. The expansion at the Baltimore site will add mammalian cell culture capacity, including a 3,000-L stirred tank reactor and a 500-L perfusion reactor, with associated purification suites. At the Hopkinton facility, Cambrex will add 3,000 L of fermentation and associated purification capacity. Both expansions are expected to be ready for clients by the middle of 2004. A second phase of expansion will add another 3,000–5,000 L of either fermentation or cell culture capacity in Baltimore, although a timeline for that expansion was not announced. The company will also begin construction on a \$5 million expansion of new laboratories and a pilot plant at its Baltimore site.

**DSM Biologics** ([www.dsmbiologics.com](http://www.dsmbiologics.com)) has also announced plans for expanding its biomanufacturing operations in Montreal. The company will add 60,000 L of cell culture capacity in two trains of 30,000 L each. Thus far, the company has authorized \$7 million for engineering studies for the project, but the DSM board of directors is expected to authorize construction later this year. **The Société Générale de Financement du Québec** ([www.sgfqc.com/fr](http://www.sgfqc.com/fr)), a government-backed investment company in Quebec, Canada, that helped finance the current DSM Biologics facility in Montreal, will also participate in the development of the new facility.

**Galen Holdings PLC** ([www.galenplc.com](http://www.galenplc.com)), has completed its exit from the contract services business with the sale of its **Interactive Clinical Technologies, Inc.** (ICTI, [www.icti-usa.com](http://www.icti-usa.com)), unit for \$16 million. The buyer was Dr. Allen McClay, the founder and former president of Galen Holdings. McClay also bought the other elements of Galen's contract services business, Chemical Synthesis Services and Clinical Trial Services.