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The dollar and other obstacles snarl the path to success of custom synthesis providers in Europe

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Over and above the business outlook that offers only cautious optimism for 2005, European producers must contend with other problems. The diminishing dollar is wreaking havoc. A discrepancy in regulatory requirements for suppliers of active pharmaceutical ingredients (APIs) based outside Europe is undermining the competitiveness of those manufacturing in Europe.

Industry insiders are concerned that not enough people skilled in science and engineering are entering the workforce.

The plunging value of the dollar is a "nightmare," says Guy Villax, chief executive officer of Hovione. "With 70% of our invoices billed in U.S. dollars, every five cents of change in the euro/dollar exchange rate wipes out \$1 million of the bottom line." Only businesses that are well managed and that have highly competitive cost bases can meet such rising costs without drowning in red ink, he adds.

The problem is mitigated by global production facilities. "If you have sites in the U.S., India, or China, where costs are based in dollars, you produce there, you pay your costs in dollars, and you sell in dollars," according to Ralf Pfirmann, senior vice president and global business director for Clariant's pharmaceuticals business unit. "We are lucky that we have dollar-based sites," he adds, pointing to Clariant production facilities in Florida, South Carolina, and



ENGAGING YOUTH

In the U.K., the chemical industry hopes to attract young people through programs like

Missouri. "But still we have a large footprint in Europe-based production."

European producers really can't do much about the weak dollar, but they are taking the bull by the horns with the other challenges. For example, to eliminate the discrepancy in regulatory requirements for API manufacturers outside Europe, European producers are demanding inspection of all manufacturers that supply APIs for drugs produced in Europe.

In the U.S., the Food & Drug Administration inspects all API manufacturing facilities to ensure compliance with current Good Manufacturing Practices (cGMP). U.S. regulations also require that all APIs coming into the U.S. must have been manufactured in FDA-inspected facilities. In fact, successful FDA inspections have become badges of honor among API producers worldwide.

IN EUROPE, pharmaceutical companies bear the responsibility of ensuring that API suppliers comply with cGMP standards, Villax explains. In theory, in a self-regulatory fashion, these companies would have inspected the facilities of their API suppliers. What happens in practice is not consistent. Reputable drug companies either audit their API suppliers or source their APIs through reputable brokers. Usually, permission to market a drug is based solely on a certificate of suitability. Issued by the European Pharmacopeia, this document certifies only that the drug product meets the criteria of the pharmacopeia, but the issuer does not inspect for cGMP compliance. "It's as if you had the FDA review without the cGMP inspection," he notes.

The bottom line is that no regulatory body inspects the facilities that make the APIs that go into drugs that end up in European pharmacies. That situation will change in October, when the European Union will implement FDA-style inspections of API facilities in Europe. However, the mandate does not extend to manufacturers outside Europe. That means Asian manufacturers still can export to Europe whether or not their facilities are inspected.

According to Villax, up to 70% of APIs used in generic drugs in Europe now come from India and China, and they enter Europe without oversight of their production by any European

Children Challenging Industry, in which companies such as Avecia host science open houses for children (top), and through the example of young chemists in industry, such as Solvay's Harper (below), the industry's young ambassador for 2004.

Credit: PHOTO BY MAUREEN ROUHI



Credit: AVECIA PHOTO

regulatory body. "European manufacturers think this is wrong from a public health standpoint and from a level-playing-field standpoint," he says.

The public health consequences are suggested by a study comparing gentamicin from various sources, carried out by Ulrike Holzgrabe and coworkers at the University of Wrzburg, in Germany [*Pharmeuropa*, **15**, 273 (2003)]. In the U.S. in 2000, 17 deaths were linked to gentamicin supplied by a China-based manufacturer. "Since these cases cannot be explained by the pharmacology and toxicology of gentamicin, it was assumed that they were related to faulty manufacture," Holzgrabe and coworkers write.

Their analysis of 39 samples of gentamicin obtained from pharmacies in Germany and the U.S. revealed seven different composition patterns. Some samples from the same drug company exhibited different composition patterns, and some results suggest that the API in the drug was not from the manufacturer claimed. An API's purity profile is central to drug efficacy and safety. The Wrzburg study shows that the purity profile is highly variable depending on the API source.

Reliance only on pharmaceutical companies themselves to ensure the quality of APIs has not been good enough for the U.S.; European standards should not be lower, Villax says.

From a business standpoint, "we can't compete with Asian products with the standards imposed on us," Villax adds. "We are asking for a level playing field. If we are going to be the subject of European enforcement, so should Asian suppliers whose APIs get into European pharmacies."

Through the European Fine Chemicals Group—a body that aims to be the voice of fine chemicals producers within the European Chemical Industry Council (CEFIC), Hovione and other API producers are appealing to the European Commission to set up an inspection system similar in authority, purpose, and function to FDA's foreign inspection service. Documents related to the issue of cGMP compliance and the consequences of noncompliance have been made available by these companies at <http://www.gmpapi.migg.com> <<http://www.gmpapi.migg.com>> .

For the long term, European industry insiders are concerned that an emerging skills gap will leave the industry bereft of the human resources it needs to move forward. Tom Shields, vice president of Avecia Fine Chemicals, sounded the alarm last November at the European Fine Chemicals Conference, held in Newcastle, England.

"It is worrying that the number of students studying science and engineering is in sharp decline," Shields said. In 2003, U.K. universities awarded 114,000 undergraduate science

degrees, compared with 160,000 nonscience degrees, he pointed out. From 1994 to 2001, acceptances to undergraduate chemistry programs dropped by 27%, whereas acceptances to business management programs rose by 55%, those to computer science programs rose by 98%, and those to media studies programs rose by 138%.

These data jibe with results of an informal survey by Rosemary Harper, a manufacturing process engineer at Solvay Caprolactones, in Warrington, England, and the U.K. chemical industry's young ambassador for 2004. She described her findings in Newcastle.

Harper surveyed U.K. students in their final two years of secondary education. She found that the most popular subjects among her respondents are psychology and information technology and the least popular is science—that is, physics, biology, or chemistry. She also found that most of her respondents did not know anyone who works for the chemical industry and cannot name a chemical or pharmaceutical company.

Despite evidence that the chemical industry offers well-paid jobs and good career prospects, "we're not attracting young people," Shields said. "Young people are preparing for careers in media, information technology, and general management rather than contributing to cutting-edge science."

What can be done? The most important step is to rebuild the industry's reputation, Shields said. Programs like Children Challenging Industry in the U.K. can help, he added. In this program, visits to chemical companies are worked into school curricula to show children and teachers how the chemical industry contributes to their everyday lives, to explain what chemists and other scientists do, and to give an idea how chemical businesses operate.

OVERTAKEN India has passed Italy in generic API production		
RANK	BEFORE 1998	1998–2003
1	Italy	India
2	India	Italy
3	Spain	China
4	China	Spain
5	Hungary	Israel
6	Israel	Hungary
NOTE: Rankings are based on the number of drug master files logged with the Food & Drug Administration during the indicated periods. API = active pharmaceutical ingredient.		
SOURCE: Arthur D. Little Benelux		

ANOTHER WAY to rebuild reputation is "to invest, create opportunities through new jobs, in the places we operate," Shields said. At its Grangemouth site, for example, Avecia is creating

opportunities through diversification. Part of the site is dedicated to biotechnology companies. Another is being developed as an industrial park for high-energy users.

"Tell them about it," is Harper's advice to the industry about attracting and retaining young people. Tell them how much pay they can expect, what career paths they can carve and how they can be supported on those paths through training and promotion, and how challenging and fun and important to everyday life are the problems they will be asked to solve. Tell them through nontraditional means, such as through young people in the industry acting as ambassadors, like Harper herself.

"Each and every one of us should be doing something to engage young people," Shields said. "If not, we will lose in what is becoming a very competitive labor market for young people."

MORE ON THIS STORY

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