VOLUME 262 NO.21 CMR DECEMBER 9, 2002

CHEMICAL MARKET REPORTER

REPORTING THE BUSINESS OF CHEMICALS SINCE 1871

Chiral Technologies Put a New Spin on the Fine Chemicals Toolbox

Major players in the custom manufacturing of pharmaceuticals continue building their toolboxes for single-enantiomer drugs. **Cynthia Challener** reports.

Pharmaceutical companies, their product pipelines dominated by single-enantiomer drugs, are outsourcing much of the development and manufacturing of these complex chiral compounds. Fine chemicals companies see this as an opportunity for growth, but they also note the challenge of providing a complete portfolio of capabilities.

According to Sandra Erb, manager, chiral & fine chemicals consulting with Technology Catalysts International (TCI), a technology consulting company, single-enantiomer compounds are the major component of the largest selling brands, in both absolute number of drugs and dollar sales volume. Total sales of chiral drugs reached $147 billion in 2001, or 36 percent of all drug sales, an increase of 10.6 percent over 2000.

Of this total, over $60 billion required some type of synthetic chiral chemistry. TCI estimates the value of the bulk active in these products at $12.7 billion, and the value of the chiral intermediate associated with these drugs at close to $7.3 billion.

Cardiovascular, antibiotics/antifungals and hormone/endocrinology are the leading categories of chiral drugs. Last year, chiral products comprised 82 percent of all antibiotics/antifungals and hematology drugs, 78 percent of cancer therapy treatments, 71 percent of hormone/endocrinology drugs and 60 percent of cardiovascular agents, according to TCI.

Worldwide Sales of Single-Enantiomer Pharmaceutical Products (Final Formulation)

	Total Market ($ in billions)		Single-Enantiomer ($ in millions)	
	2000	2001	2000	2001
Cardiovascular	46.6	50.0	27,650	30,169
Antibiotics / Antifungals	31.7	33.0	25,942	26,873
Hormone/Endocrinology	22.0	26.0	15,228	18,474
Cancer Therapy	15.6	17.0	12,201	13,286
Central Nervous System	53.9	55.0	9,322	10,498
Hematology	15.4	16.5	11,989	13,466
Antiviral	19.1	20.0	5,890	6,102
Respiratory	40.5	42.0	6,506	7,875
Gastro-Intestinal	47.2	50.0	4,171	5,411
Ophthalmic	7.4	8.0	2,265	2,434
Dermatological	18.4	18.5	1,272	1,187
Analgesics	23.0	23.5	1,199	1,206
Vaccines	7.3	8.5	3,447	4,299
Other	41.9	42.0	5,929	5,848
Total	**390.0**	**410.0**	**133,011**	**147,128**

Source: Technology Catalysts International

Rhodia ChiRex's Dudley, UK, cGMP pilot plant. The company has licensed numerous chiral technologies developed by academic research groups.

The overall fine chemicals merchant market is estimated to be $24 billion/year and is expected by analysts to grow at 5 to 8 percent per year, an increase from the 3 percent growth observed in 2001. This market includes contract manufacturing of drug intermediates and active pharmaceutical ingredients (APIs), which encompasses chiral chemical manufacturing. Growth in chiral technologies is expected to outpace the general fine chemicals market.

Biological processes—fermentation and enzymatic transformation—are also used to produce chiral compounds. According to Enrico Polastro, senior industry specialist, Arthur D. Little (Brussels), the market for such biopharmaceutical manufacturing totals approximately $500 million, while the market for biopharmaceutical development services (excluding licensing agreements) is valued at $200 million. TCI estimates that the merchant market for biocatalysts used for fine chemical/pharma applications at $120 million to $150 million in 2001, with growth of 8 to 9 percent.

Selected Licensing Agreements in Chiral Technologies

Licensor	Licensee	Technology
Harvard University	Rhodia Chirex	Jacobsen's hydrolytic kineticr esolution system for the synthesis of diols and epoxides.
Harvard University	Rhodia Chirex	Jacobsen's asymmetric epoxidation technology for conversion of cis-olefins to corresponding epoxides.
Harvard University	Rhodia Chirex	Jacobsen's amino acid technology for amino acids and derivatives from aldehydes.
Harvard University	Rhodia Chirex	Jacobsen's asymmetric ring opening technology for conversion of meso epoxides to chiral azido alcohols that can be reduced to amino alcohols.
Scripps Institute	Rhodia Chirex	Sharpless' asymmetric dihydroxylation technology for synthesis of chiral diols from olefins.
Seprachem	Rhodia Chirex	Asymmetric reduction technology using aminoindanol based oxaborazolidine catalysts to reduce prochiral ketones to alcohols.
California Institute of Technology	Strem	David MacMillan's chiral Diels-Alder catalysts for research use.
California Institute of Technology	Sigma-Aldrich	David MacMillan's chiral Diels-Alder catalysts for research use
California Institute of Technology	Materia (Pasadena, CA)	David MacMillan's chiral Diels-Alder catalysts industrial use
Dow/Chirotech	Strem	FerroTane catalyst for asymmetric hydrogenations
Chiral Quest	Varsal	Technology for production of beta-amino acids and chiral building blocks
Aventis Pharma	Synetix	Ferrocenyl phosphine ligand JAFAPhos used in asymmetric allylic alkylations, grignard cross-couplings and aldol reactions — to develop economical and scaleable route to ligand and investigate using ligand with immobilization technology.
Hong Kong Polytechnic University	Synetix	
Yale University	Synetix	Will develop and commercialize phosphine ligands - adamantly/ pentaphenylferrocenyl ligand for Heck and Suzuki reactions and Pd BINAP catalysts for enantioselective hydroamination.
Roche	PPG-Sipsy	MeOBiphep - 2,2'-bis (diphenyl-phosphino)-6,6'-dimethoxybiphenyl
Center for Applied Catalysis at Seton Hall University	Johnson Matthey	Robert L. Augustine's asymmetric homogeneous catalysts anchored on alumina, silica or clay supports using heteropolyacids.
Nagoya University	Avecia	Noyori catalysts for used in CATHy transfer hydrogenation processes
Merck & Co	Synetix	PhanePhos hydrogenation ligand—will develop commercial route and then also use with immobilization technology.
Penn State University	DSM/Catalytica	PennPhos ligand
Colorado State University	DSM	BICP and Epoxone ligands
DuPont	Dow/Chirotech	Chiral DuPhos/BPE asymmetric hydrogenation ligands for use in pharma, flavor and fragrance industries; ligand for Trost palladium and molybdenum catalysts for asymmetric allylic substitution.
Japan Science and Technology Corporation	Dow/Chirotech	Noyori/Ikariya technology for the asymmetric hydrogenation of ketones to chiral alcohols using ruthenium catalysts.
Merck & Co.	Dow/Chirotech	PHANEPHOS ligand
Stanford University	Dow/Chirotech	Trost's palladium and molybdenum catalysis technologies for asymmetric allylic substitution.
Harvard University	PPG-Sipsy	Corey's oxazaborolidine for asymmetric hydroboration of ketones to optically pure secondary alcohols.
Scripps Research Instiute	PPG-Sipsy	Sharpless asymmetric epoxidation of allylic alcohols

Source: CMR research

Major fine chemicals players agree that a chiral toolbox is key. "Fine chemicals manufacturers operating in the pharmaceutical sector, and increasingly also in the agrochemical and non-life science sectors, are today expected to offer the widest range of chiral technologies, using synthetic chemistry and biotechnology platforms," says Karlheinz Drauz, vice president technology and R&D management with the fine chemicals business unit of Degussa AG. "Mastering as many chiral technologies as possible is thus essential for success." Ron Carroll, vice president & chief technology officer, pharmaceutical technologies with Cambrex Corp., agrees. "Broad chiral technical capabilities combined with a good customer service reputation of delivering on time, cost effectively and providing high quality product are necessary to compete effectively," he says.

"The opportunities are mainly due to the large and increasing market size for chiral intermediates and the relatively immature technology base for the preparation of these intermediates," notes Neil W. Boaz , senior research associate with Eastman Chemical Company. These opportunities are tempered by the current overcapacity in the batch chemical manufacturing industry, he says. "Having advantaged technology is crucial for success, and this drive for advantaged technology is the most obvious trend in chiral technologies."

But the market for chiral technology is increasingly crowded. For Alan E. Walker, director of marketing & development for the fine chemicals division of Kaneka America Corp., the key challenge is the increasing number of players in the chiral technologies field without a corresponding increase in the market size. The demand for pharmaceuticals (the major market for chiral compounds) has fluctuated, he notes, product pipelines are not as full as in the past, and the final drug targets are becoming more unique and complicated. In addition, the recent slowdown and uncertainty of the regulatory approval process continues to have an impact. "To be able to deal with such challenges the players in the field are having to arm themselves with broad and deep technology portfolios that allow them to tackle as diverse a range as possible of new drug development candidates," says Mr. Walker.

At the same time, manufacturers not only have to have such technology but also have to demonstrate that they can use it efficiently in a commercial environment. "Drugs are becoming increasingly diverse and complex, and the appropriate integration of chiral technology into complex synthetic sequences is an important capability in itself," says David J. Moody, director of new technology ventures for Avecia Pharmaceuticals. However, "excellence in a given type of transformation is not enough. Application of appropriate chiral solutions is critical."

Nick Hyde, business director of pharmaceutical services with The Dow Chemical Company, agrees. "Success for manufacturing companies in asymmetric catalysis is likely to depend on their ability to embrace the methodology within their process chemistry," he says, "and to integrate with other capabilities such as multistep organic synthesis and process engineering to form a complete solution, rather than from having asymmetric catalysis technology by itself."

Providers of chiral technology need to establish scientific and business models that offer the highest degree of flexibility, says Peter C. Michels,

senior director of Albany Molecular Research Inc.'s (AMRI's) Mount Prospect Research Center. He believes that over-concentration in specialized approaches is a critical issue for chiral technologies. "Technology companies need to have a wide spectrum of capabilities and have the appropriate resources necessary to design appropriate chiral chemistry for a specific task."

Part of the problem is that many asymmetric technologies lack generality, observes Thomas Archibald, vice president of research and technology with Rhodia ChiRex. Small changes in impurities, solvents, catalyst structure, and many other parameters can affect yields. High-throughput screening done by many companies can be useful in finding the best combinations of conditions, but challenges often occur in scale-up after a catalyst system is selected.

"These systems are often 'technologically handicapped', in that they require the use of reagents or methods that are difficult on a large scale," says Mr. Archibald. "Examples are high pressure or temperature, air or moisture sensitivity, exotic reagents or catalysts and specialized or high-purity solvents." Mr. Archibald notes, though, that more than 70 percent of Rhodia Chirex's development projects involve chiral reactions. "Clearly, this technology and this market remain important."

Chiral technologies need to be even more stereo- and enantiospecific, says Jean-Claude Caille, director of innovation and development for PPG-Sipsy. They need to provide higher diastereomeric and enantiomeric excesses with very low catalyst substrate ratios and high turnovers. "The catalysts which are currently being developed will need to behave like enzymes," Mr. Caille notes. "In addition they will need to be relatively simple to avoid complex and costly preparations." Many chiral diphosphine ligands have been discovered in the past years, he adds, but new concepts need to be proposed to create new generations of catalysts.

Selected Agreements and Alliances

Partners	Activity
Avecia and Synetix	Synetix immobilizing catalytic asymmetric cyanohydrin (CACHy) and transfer hydrogenation (CATHy) catalysts.
Rhodia Chirex and Synetix	Synetix successfully immobilized Co(salen) catalyst for hydrolytic kinetic resolution and was making chiral forms of epichlorohydrin, propylene oxide, methyl glycols on a commercial scale mid 2002.
Dow/Chirotech and Acros Organics	Acros will market research quantities of Chirotech's range of chiral organic advanced intermediates, unnatural amino a ids and scaffolds worldwide.
Rhodia Chirex and Sigma-Aldrich	Sigma-Aldrich will sell Chirex's ligands and catalysts for Sharpless asymmetric dihydroxylation reactions.
Degussa and CalTech	Frances H. Arnold of CalTech developed with Degussa a new method using hydantoinase technology to produce L-amino acids.
Lancaster and Toray Ind.	Lancaster will include Toray's chiralpyrroldines in its catalog.
Avecia, King's College, Nesmeyanov Institute	Development of CACHy catalytic asymmetric cyanohydrin technology.
University of Bristol and Avecia	Development of ylide chemistry invented by Varinder K. Aggarwal to make single enantiomer cyclo propanes, epoxides and aziridines.
Avecia and IBC Technologies	Co-fund development of molecular] recognition technology (MRT) for chiral separation.
Dow/Chirotech and Diversa	Nitrilase Chemistry
Chiral Quest and Clariant	To develop catalysts for asymmetric synthesis of APIs.
Cambrex and Synthon Chiragenics	Development of a series of proprietary chiral libraries for sale to combinatorial and pharmaceutical companies.
Johnson Matthey/Synetix	Johnson Matthey is acquiring Synetix, including its immobilization technology for chiral catalysts.

Source: CMR research

Degussa's Raylo facility in Edmonton, Alberta, Canada.

New technologies are being developed all the time, with most players focusing on new catalytic techniques in recent years. Dr. Lucian Boldea, business market manager with Eastman Chemical Company notes that "the development of commercially viable and scalable chiral catalyst systems has brought a whole new set of technologies to the marketplace and has complemented nicely existing technologies involving biotransformations or chiral separations."

For example, PPG-Sipsy's Mr. Caille points to the useful chiral diphosphine ligands discovered by H. Kagan in France (DIOP) and R. Noyori in Japan (BINAP and SEGPHOS). "These ligands have turned out to be quite revolutionary when used for asymmetric hydrogenation," he says. Mr. Caille also notes that Prof. Kagan's pioneering work on asymmetric amplification has lead both academic and industrial chemists to better understand chiral reactions. He adds that the Sharpless epoxidation and dihydroxylation have provided chemists with exceptional tools in the field of oxidation, despite some serious limitations at commercial scale.

Biocatalysis has proved to be an important alternative to classical approaches. For Degussa's Mr. Drauz, important current developments in chiral synthesis include the progress in biocatalysis through genetic engineering and evolutionary methods as well as new and improved asymmetric reduction of multiple bonds. "In the last decade biotechnology and especially biocatalysis developed faster |and broader than classical chemistry. Directed evolution in combination with many genomic projects and the rapid increase of knowledge in proteomics might be finally superior in quite a lot areas which have been a domain of classical organic chemistry," says Mr. Drauz. "The design of metabolic pathways, [the] combination of different genetic information in one production strain (for discrete molecules as well as for functional proteins) will provide us with superior processes and will open an area of real economically and environmentally favorable processes."

Specific examples of top developments in biocatalysis from Degussa's perspective include kinetic dynamic enzymatic resolution systems in which a racemate can be transformed in one pot and *in situ* completely into the desired single enantiomer without any external racemization; cofactor dependent enzymatic reactions such as oxidations, reductions and some lyase reactions; new isomerase catalyzed reactions; highly effective, stable and cheap hydrolases for cost effective processes; and the expression of mammalian enzymes in microorganisms.

AMRI's Mr. Michels also focuses on the field of enzyme catalysis when discussing technological advances in chiral synthesis. In addition to dynamic kinetic resolutions, he points to approaches for directed evolution to refine and improve the stereoselectivity of enzyme catalysts for target syntheses and advances in

Rhodia ChiRex has licensed Eric Jacobsen's hydrolytic kinetic resolution, an efficient route to chiral epoxides and diols.

genomics to enable access to additional and often novel enzyme catalysts.

Another important advance has been the immobilization of homogeneous chiral catalysts, according to Avecia's Mr. Moody. "Immobilization enables the avoidance of metal contamination, recycle of catalysts and continuous manufacturing technology," Mr. Moody points out.

Custom enzymes and chromatographic separation have made extraordinary progress. From Cambrex's point of view, the best technology advances also continue to be in the area of custom enzymes, whereby point mutations and combinatorial enzyme generation allow identification of an enzyme specific to a needed transformation. Mr. Carroll also points to the development of advanced chromatographic separation techniques that allow commercial scale production as critical new technology. Chromatographic separation techniques will become more and more important with the continued development of high potency and naturally derived active pharmaceutical ingredients, he explains.

The Nobel Prize awarded to Sharpless, Knowles and Noyori for their work in asymmetric oxidation and asymmetric hydrogenation has put chiral technology in the spot light, says Dow's Mr. Hyde. "This award should give the chirotechnology field a much greater presence in the wider scientific community," he says. Prof. Noyori is on the Technology Advisory Board of Chirotech Technology Limited, which is now part of Dow's Pharmaceutical Services business.

As molecules in the life science sector become more complex in structure, the use of asymmetric synthesis as a means to control the introduction of further stereocenters in molecules with one or more existing chiral carbons will be increasingly valuable, according to Mr. Hyde. "That way we can maybe make asymmetric synthesis have an impact where it really matters—when a new drug is discovered," he notes.

Building the chiral toolbox has often meant going outside the company. As the need for access to a complete set of chiral technologies has grown, companies have increased efforts to enhance their capabilities through external relationships with other organizations. The number of alliances and licensing arrangements has steadily risen over the past several years. Major players in chiral technologies have found that bringing in technology to complement their own research and development efforts is an effective strategy for building the necessary broad-ranging program so critical to success.

For example, Rhodia Chirex has licensed technology from professors Stephen Buchwald at MIT, Eric Jacobsen at Harvard, K. Barry Sharpless at Scripps Research Institute and others. According to Mr. Archibald, catalysts or technology can be developed through an in-house or contracted research program, technology can be licensed from universities, or catalysts can be purchased from suppliers, in which case the royalties are included in the purchase price of the catalysts.

"A balanced approach makes most sense. A company should develop a portfolio of technologies, and as the opportunity arises, the tool box should be expanded," says Mr. Archibald. "Customer needs are identified in the form of real projects. When a project is found, the technology base of understanding is developed around the specific target and then generalized to other targets."

Avecia believes that licensing of technology should be an important feature of growing a powerful technology portfolio. "No single company is big enough or smart enough to invent all the technology it needs," says Mr. Moody. "Partnerships between manufacturers and technology providers can be highly successful, given realistic expectations, value sharing and commitment." Avecia is continuously looking for good opportunities to license differentiating technology and will maintain this activity as a key element of its strategy.

Licensing out can be as profitable as licensing in. Eastman has a number of relationships with business and academia that have had a positive influence on new developments in the chiral technologies area, says Boldea. In addition, the company is licensing its BoPhoz technology to others. "We have taken a novel approach to licensing that offers our customers added flexibility," says Mr. Boldea. "The license is included with the purchase of the molecules for customers who wish to conduct their own reactions. Or they can have Eastman conduct the reactions."

PPG-Sipsy has licensed from a Swiss company a diphosphine ligand useful in asymmetric hydrogenations. The company also licensed from Harvard University Corey's asymmetric reduction catalyst, an oxazaborolidine for asymmetric hydroboration of ketones to optically pure secondary alcohols. According to Mr. Caille, PPG Sipsy has several ongoing collaborations with universities worldwide. Bayer, too, has strong relationships with external collaboration partners at both universities and smaller companies to broaden its scope, says Christian Militzer, senior manager, R&D, fine chemicals. "We make these forward-looking types of investments in projects that we expect to give us results in the long term," he notes.

"Whenever necessary we are prepared to license in pieces of chiral technologies (eg. catalysts, ligands, asymmetric procedures) to complete our existing technology platform," says Degussa's Mr. Drauz. "From our cooperation with university groups we get a constant 'Zufluss' (flow) of new results, which we patent together." Examples are Degussa's new Malphos-Catalyst, which was developed and patented together with Professor Börner of IFOK Rostock (Institut für Organische Katalyseforschung, Research Institute for Organic Catalysis), and the new recombinant PLE (pig-liver-esterase), expressed in a microbial production strain, which was discovered jointly with the group of Professor Bornscheuer at the University of Greifswald.

Through its integration of Chirotech, Dow Pharmaceutical Services has built a chiral chemistry capability derived from a combination of technologies discovered in-house and through licensing from a range of organizations—corporate, academic and governmental, says Mr. Hyde. Amongst in-licensed technologies, asymmetric hydrogenation features heavily, notably the DuPHOS ligands and catalysts licensed from Dupont (exclusive for pharmaceuticals) and Noyori's ketone hydrogenation licensed from the Japan Science and Technology Corp., into which the PhanePhos chemistry licensed from Merck has been successfully leveraged.

Considerable effort has also been made at Dow to establish a capability in catalytic asymmetric C-C and C-heteroatom bond forming reactions, through a long-standing relationship with Barry Trost and Stanford University, resulting in exclusive licenses to palladium- and molybedenum-catalysed asymmetric allylation technologies and a new license secured in 2002 for Prof. Trost's asymmetric aldol technology. "In offering this broad array of technologies, we seek to be the first-choice provider of asymmetric hydrogenation technology, already embraced by our customer base, and to foster acceptance of newer technologies for structurally complex targets," explains Mr. Hyde.

Cambrex continues to look at new technologies that can be purchased, licensed or partnered. "Our guidelines are that the new technologies have to be differentiating, reasonably broad based and cost effective. We seek technologies that also have a portfolio of commercial products available that are produced by the technology. The Cambrex approach is a measured one in that technology and profitability drive our decisions," says Mr. Carroll. The company continues to modify technologies that it already owns (i.e. its transaminase enzymes) for specific efficiencies that impact operations related to molecules being commercialized. CMR