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Custom chemicals makers stress chiral technologies

By Gordon Graff -- 7/18/2002

Some of the fastest growing new drugs today are chiral molecules—those which can exist as two mirror-image isomers. Chemically, they are single enantiomers, with each of their molecules being one half of a pair of mirror-image isomers. As drugs, single enantiomers often exhibit greater potency and cause fewer side effects than do more conventional drug molecules, which may be chiral but are often equal-parts mixtures of both enantiomers. As a result, chiral technology—the process of synthesizing or isolating chiral molecules and their single enantiomers, has become big business for a legion of catalyst developers and custom chemical manufacturers.

Global revenues from chiral technology will soar from $6.63 billion in 2000 to $16.03 billion in 2007, growing at a compound annual rate of 13.4% during that period, forecasts the market research firm Frost and Sullivan. The pharmaceutical industry accounted for 81.2% of chiral market revenues in 2000, the company reports; agricultural chemicals made up 14.1% of the revenues; and flavors and fragrances accounted for 4.7%.

Approximately 80% of all products currently in development for the pharmaceutical industry are based on chiral building blocks, according to Karlheinz Drauz, vice president for technology and R&D management in the fine chemicals business unit of Degussa AG in Hanau-Wolfgang, Germany. Many single-enantiomer chiral drugs have recently hit the market. Among the more successful ones are AstraZeneca's stomach acid remedy Nexium, GlaxoSmithKline's anti-anxiety agent Paxil, and Merck's asthma drug Singulair.

Regulatory pressures

The quest for more potent and effective drugs isn't the only factor driving pharmaceutical industry interest in chiral technology. Recent changes in rules at regulatory agencies such as the U.S. Food and Drug Administration and the European Committee for Proprietary Medicinal Products require that all isomer components of new drugs be completely characterized. As a result, "there's been a tendency for pharmaceutical companies to go with single enantiomers," says Sandra E. Erb, manager of chiral and fine chemical consulting at Technology Catalysts International, Falls Church, Va. The reason, she explains, is that "they don't want to bother to isolate each enantiomer and go through all the toxic studies."

Chiral technology is being enlisted to develop new agricultural chemicals such as pesticides and weed killers. But high development costs in this sector and the absence of the same regulatory pressures facing pharmaceuticals mean ag-chemicals "is not going to be a very important market" for chiral technology in the long term, says Erb. Chiral chemistry has also had some success in development of synthetic flavors and fragrances. But Erb believes that growth in this application may be limited by consumers' preferences for extracts of natural products, rather than totally artificial molecules that would require chiral technology.

Chiral technologies involve several methods (see table). One of the oldest, and still widely practiced, approaches is to use chiral chemical catalysts or enzymes to separate (or resolve) equal-parts mixtures of both enantiomers of chiral molecules. This is, however, time-consuming and expensive; it is also wasteful of resources because the unwanted enantiomer of the molecule (usually half the batch) is typically discarded. A more recent method, and one that is at the forefront of the field, is to use specially developed chiral chemical catalysts or biocatalysts (enzymes) to synthesize just the desired enantiomer. This eliminates the need to separate the two forms of a chiral molecule, along with the waste of unwanted byproducts.

Purveyors of chiral products and services make money in a variety of ways. They may license out their proprietary catalyst technologies to large drug or chemical firms, or the custom manufacturers to whom those firms outsource their manufacturing. They may use chiral catalysts—either their own or licensed ones—to synthesize chiral building blocks for customers, who then incorporate these vital fragments into larger molecules. But increasingly the trend is to offer a complete suite of services that includes research, custom synthesis and process development. Customers can then pick and choose the services that meet their needs.

Dow Chemical's Chirotech Technology Ltd. subsidiary, which it acquired in the spring of 2001, is developing a host of new catalytic methods for chiral technology. The firm, based in Cambridge, U.K., uses proprietary chemical catalysts for asymmetric hydrogenations such as conversion of ketones to chiral secondary alcohols. It employs biocatalysts for other tasks, such as production of "unnatural" amino acids (opposite enantiomers to the naturally occurring ones). The company also has an R&D program to develop chiral catalysts that can produce molecules with more than one chiral center. Chirotech licenses catalysts, does custom synthesis, and, in conjunction with other branches of the Dow organization, offers process engineering. "Being able to put all these diverse pieces together is what gives us our competitive advantage," says Raymond McCague, research and technology director at Chirotech.

BASF, which has a line of chiral chemical intermediates known as ChiPros, also offers custom synthesis and process scaleups. In late 2001, the company opened two facilities to make chiral pharmaceutical building blocks, including a 1,000 metric ton/year plant in Ludwigshafen, Germany, to produce its ChiPros amines and secondary alcohols, and another multi-ton facility at the same location to manufacture mandelic acid. In 2001 the firm also dedicated a 2,500 metric ton/year plant in Geismar, La., to produce a chiral intermediate for its herbicide Outlook. BASF offers process development services to its chiral intermediates customers, with production volumes ranging from "grams to tons," says Karl Klein, BASFS director of business development for chemical intermediates.

Degussa is active in chiral technology on many fronts. Early this year the company introduced its new L-hydantoinase enzymatic process for single-step production of L-amino acids from chemical precursors. The firm has developed other enzymatic processes for producing chiral alcohols, amines, organic acids, amino and hydroxy acids. R&D goals in Degussa's chiral program include the manufacture of single-enantiomer amino acids and peptides and derivatives made from them. The company also has several internal basic research efforts, known as Project Houses, which include programs in high-throughput screening of chiral catalyst candidates and the optimization of new chiral biocatalysts. Given the complexity and diversity of new chiral drug molecules today, Drauz believes that "mastering as many chiral technologies as possible is essential for our success."

Upgrading molecules

Rhodia ChiRex, Boston, Mass., the chiral product and process development arm of the Paris-based chemical giant Rhodia, has recently scaled up to commercial size its capabilities in a chiral process called hydrolytic kinetic resolution. The technology, licensed from Harvard University, where chemist Eric Jacobsen developed it, offers an efficient route to various chiral diols and epoxides that are key building blocks for pharmaceuticals. The company is developing additional chiral technologies discovered by Jacobsen and other outside researchers. Among these processes are asymmetric reductions, dihydroxylations, epoxidations and ring openings. Rhodia ChiRex's services include contract research, process development and manufacturing for pharmaceutical customers. The newly commercialized hydrolytic kinetic resolution process is important because "it allows you to take a relatively inexpensive small molecule and elaborate on it chemically in many directions to make far more valuable molecules," says Tom Archibald, vice president for research and technology at Rhodia ChiRex.

Fine chemicals producer Avecia, Manchester, U.K., has a broad portfolio of chiral technologies. The company's catalytic asymmetric transfer hydrogenation process, dubbed CATHy, offers a route to chiral alcohols and amines, while its carbon-carbon bond forming technology, known as CACHy, is said to improve the economics of chiral cyanohydrin synthesis. Currently under development at Avecia, with partner IBC Advanced Technologies, is a technique called molecular recognition technology, which is being positioned as a higher yield competitor of traditional HPLC (high-performance liquid chromatography) for separating mixtures of chiral compounds. At last February's Informex trade show in New Orleans, Avecia announced a research partnership with Synetix Chiral Technologies, a unit of ICI, to develop immobilized versions of its transfer hydrogenation and cyanohydrin catalyst systems. Avecia says that the immobilized systems would allow for continuous-operation processes, eliminate catalyst impurities in products, and potentially increase catalyst yields.

While forecasters say pharmaceutical markets will dominate chiral technology development for the foreseeable future, other promising outlets are on the horizon. One is optical communications. According to Erb of Technology Catalysts International, some advanced optical devices require single enantiomers of chiral inorganic crystals to propagate light waves. And Drauz of Degussa sees important future applications of chirals to produce more potent versions of food additives, nutraceuticals and cosmetic products, including vitamins, amino acids, special lipids and other natural compounds.