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Chirality Companies Broaden Their Approaches

Successful Firms Expand Beyond Single-Carbon Transformations

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Chirality continues to loom large for new drug development as small-molecule drugs become pharmacologically more specific, and therefore more structurally complex. Since therapeutic targets are usually chiral, new drugs must strive to match their asymmetry, as well as their chemistry and topology.

When drugs exist as two enantiomers, one isomer is generally, but not always, more active than the other; in some cases one isomer is inactive or even harmful. Single-enantiomer drugs therefore offer the potential to achieve the same or greater therapeutic effect as racemates, but at lower effective doses and with fewer side effects.

Although single-enantiomer drugs are often more expensive to produce, at least initially, they offer potential economic benefits down the road, such as greater safety, smoother regulatory approval, and extended product life cycle.

At one time it appeared that the FDA would take a hard-line stance on chirality. The agency, however, has not substantially changed its position on chirality since the release of “Policy Statement for the Development of New Stereoisomeric Drugs,” a 1992 guidance document outlining the agency’s suggestions for testing individual enantiomers.

Ordinarily, FDA requires toxicology testing for racemates only, even if a company plans to market a sinle isomer. If unexpected or significant toxicity is found in the racemate, FDA suggests querying the agency on whether similar studies are required of the enantiomers.

For chiral switches, FDA suggests a pharm/tox evaluation to show that the enantiomer is no more toxic than the racemate and has a similar pharmacokinetic profile. The agency also suggests collecting data on enantiomeric interconversion, when appropriate.

Whatever FDA’s position, single-isomer drugs are here to stay, as are markets for both chiral intermediates and development services. According to Technology Catalysts (Falls Church, VA), sales for single-enantiomer pharmaceuticals rose to $115 billion in 1999, up 16% from the previous year. Worldwide sales of pharmaceuticals were about $300 billion that same year.

Technology Catalysts expects chiral drug sales to increase by 8% per year through at least 2003. The worldwide pharmaceutical market was valued at $360 billion in 1999.

Cost of Doing Business

At one level, single-isomer drug development may be viewed as another obstacle for pharmaceutical developers already burdened with lengthy approval times and high development costs.

"Costs associated with getting NCEs (new chemical entities) to market have gone through the roof," says Michael Ratchford, vp of business development at Oxford Asymmetry (Abingdon, U.K.). "At one point, companies expected to get two or three NCEs on the market each year, but most have been lucky to get one. Wall Street has not been happy with this performance."

Sandra Erb, an analyst with Technology Catalysts, agrees. "Cost pressures on the pharmaceutical industry have reached unreal proportions. Companies are no longer guaranteed profits since governments and insurers have clamped down on medical costs. As a consequence, it has become more difficult to solve problems by throwing money at them."

Single-enantiomer development has not improved the overall outlook for getting NCEs approved, as some predicted. "We're seeing a lot of failures among chiral drug candidates," a fact Erb attributed to the pressure on both pharmaceutical companies and FDA to push drugs through approval. "Failure has nothing to do with chirality. Everyone wants drugs approved faster, but everyone also wants these products to be as safe as when approval took longer. We're also seeing a lot more drugs pulled during Phase III or even later."

Consolidation

Chirality and related services by themselves have not offered service companies the kind of growth usually expected in the pharmaceutical sector. No matter how proprietary a chiral process may be, there is almost always a way to work around it. Faced with costly licensing arrangements or partners they don't want or feel they need, drug firms will do whatever they can to employ nonproprietary chiral technology, purchase off-the-shelf chiral intermediates, or simply market the racemate.

"Sure, companies will sometimes spend whatever it takes to get the first kilo or so of a new chiral drug. But while early clinical and preclinical testing is going on, you can be sure they're figuring out a way to get their material more cost-effectively and without exorbitant licensing fees for chiral technology."

Eventually, relatively inexpensive chiral building blocks purchased from catalogs or through custom synthesis may reduce the need for chiral chemistry know-how to the same level as that for other specialty chemical expertise.

Chirality's tough business play is reflected in the recent consolidation among chirality specialty firms. By the time ChiRex was acquired by Rhodia (Paris), and Catalytica by DSM Biologics (Groningen, The Netherlands), both acquirees had become contract manufacturers with world-class capacity. Chirotech's acquisition by Ascot plc (London) reflected a similar desire to expand into manufacturing.

Shortly after Ascot's purchase of Chirotech, ChiroScience, Chirotech's former parent company, merged with Celltech to become Celltech Chiroscience (London), a discovery-stage biopharmaceutical company. Similarly, Oxford Asymmetry's merger with Evotec Biosystems (Hamburg, Germany) strengthened both forms' discovery and development-stage services.

Despite its name, Oxford did not remain a pure chiral company for long. Founded in 1992 by Professor Steven Davies of Oxford University, the company began offering a catalog of chiral intermediates, a business it maintains to this day. "But seeing much broader needs in the marketplace, we developed more of a full-service business model," says Ratchford.

In 1994, management decided to expand its services to include general route selection, kilo-scale synthesis, and pilot-scale GMP development, as well as a discovery chemistry business. Oxford's business then took off, growing by 35% per year since.

Like all successful mergers, Oxford/Evotec combines complimentary technologies, in this case Oxford's synthesis with Evotec's discovery and screening capabilities. Today, Oxford espouses a "target to lead" philosophy. "You give us a target," Ratchford states, "and we'll get you a lead and enough material to get through Phase I studies."

Extending Patent Protection

Chiral switches, patenting, and marketing chiral versions of recemic drugs remain a viable strategy for extending the product life cycle. AstraZeneca's (London) development of a single-enantiomer form of its racemic Prilosec (omeprazole) antiulcer drug is perhaps the most prominent recent example. Racemic omeprazole was approved in the U.S. in 1995 but its patent expires this month.

The (S)-isomer, branded as Nexium (esomeprazole) and containing most of the compound's activity, was approved in Europe in July 2000 and received the FDA's OK three months ago. As AstraZeneca's $5.9 billion (1999) sales from Prilosec begin falling over the next few years because of generic competition, sales of esomeprazole will help soften the blow.

Schering-Plough (Kenilworth, NJ), for example, will stick with the branded, racemic version of its popular Proventil (albuterol) asthma drug rather than license the single-isomer switch developed by Sepracor, which eventually teamed with Abbot Laboratories (Abbott Park, IL) to market levalbuterol.

The success of chiral switches is by no means guaranteed, however. Health maintenance organizations pressure physicians to prescribe generic drugs whenever possible, threatening to expel them from their networks if they persist in prescribing newer, more expensive pharmaceuticals. That could spell trouble for chiral-switch developers, who expected an easy time getting their new, improved products accepted.

Lure of Technology

Building a business around chirality is still possible, but to succeed, companies must specialize beyond single-carbon chiral transformations. **Synthon Chiragenics** (Monmouth Junction, NJ), for example, focuses on carbohydrate-derived chiral intermediates. Because of its raw materials' built-in chirality and chemical functionality, Synthon has access to advanced intermediates and such drug substructures as chiral imino sugars, amines, lactams, and oxazolidinones.

"Our company began as a chirality company, and chirality is still a big part of our business," explains Wayne Weiner, Ph.D., director of marketing. "But here's the difference, our technology creates multiple, contiguous chiral centers, and it's scalable."

Multiple chiral centers and rich functionality are hallmarks of next-generation drugs, according to Rawle Hollingsworth, Synthon's founder and CSO. "Many of the new drugs of the post-genomic era will look a lot like DNA," he explains.

"You can't design all that chirality into a molecule, on a manufacturing scale, unless you already have it built in. Sure, you can achieve it through 25 steps, but that won't cut it during manufacturing. It so happens that the molecules that people need help with are complex, chemically challenging, and most often chiral. We focus on those projects."

Like other chemistry service companies, Synthon does not mind getting into royalty arrangements with customers. "We like to work much closer to the final molecule, and we have a lot of technology to back up that desire," Hollingsworth says, "However, we don't try to over-leverage our position. In some cases our chemistry indeed saved the day, but our focus is not on getting the credit, it's on getting the work done."

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