For the last decade, drug discovery programs have turned to specialized suppliers of historical compound and combinatorial libraries to feed high-throughput screening's impressive appetite for chemical novelty.

The mapping of the human genome, by providing a myriad of new targets, will greatly sharpen that appetite and shift the drug discovery bottleneck further toward chemical synthesis. Demand will increase for screening libraries that can widen the scope of chemical diversity by offering more complex and novel compounds. Glaxo Wellcome offers one example of a major pharmaceutical company's evolving relationship to suppliers of screening libraries. David Langley, compound acquisition manager at Glaxo Wellcome R&D, Stevenage, UK, says that the company turned to compound suppliers in part to overcome the limitations of its existisng libraries, which had not been produced for high throughput screening (HTS) but was largely the by-product of discovery efforts. Over 80 percent of the collection had consequently been synthesized in-house, and its chemical diversity was limited. Further a significant portion had to be eliminated as inappropriate for screening. The resulting collection, though useful, was relatively small-many authorities believe that a completely random library must have at least 250,000 members to provide good coverage of the chemical space-and it would not be replenished in house as quickly as it was used. It therefore needed to be augmented.

Facilitating Glaxo Wellcome's acquisition efforts have been the many specialist suppliers in the market for high throughput screening libraries. Rijswijk, the Netherlands-based SPECS may have been the first. About 10 years ago, the company began canvassing the newly - accessible universities and research institutes of the former Soviet Union for novel chemical entities. Comgenex, a Hungarian company, and Russian companies such as Contact Services and AsInEx soon emerged to follow suit. Since then, an entire industry has sprung up to manufacture by conventional synthesis drug-like compounds for screening. By one count, as many as 6,000 chemists in the former Soviet Union are engaged in such activity Meanwhile, suppliers in North America such as ChemBridge (San Diego, Calif.) and Timtec (Wilmington, Del.) have brought supplies and services closer to stateside customers, and new suppliers continue to appear in Russia and Eastern Europe. GlaxoWeilcome has received innumerable catalogs totaling 1.8 million unique structures, and new ones arrive daily.

Suppliers provide these molecules for a fraction of what they would cost as synthetic targets-just $10 to $50 for 10 to 20 milligrams. They generally prescreen the structures to ensure that they are suitable fur high throughput screening. They also take care of practical aspects, for example delivering samples in vials, on plates, in solution, pre-weighed or bar-coded. Such a trove cannot be ignored, particularly given that competing drug companies have their own HTS programs.

At the same time, a rival supply of screening libraries has evolved parallel to the suppliers of hand-made molecules: these are the combinatorial chemistry companies, who integrate the speed of high throughput robotics with extremely efficient chemistries to rapidly produce extensive collections of structural analogs.

Glaxo Wellcome has not turned to combichem suppliers, says Mr. Langley, partly because it has bug had a substantial in-house effort. In 1995, Glaxo Wellcome became one of the first major pharmaceutical companies to invest in combinatorial chemistry when it bought Mffymax

for $500 million. But GlaxoWellcome also relies on historical compound libraries because hand-made molecules offer extraordinary chemical diversity.

"When we asked customers what they need, they said, 'We don't know, just give us different chemistries," says Murat Niyazymbetov, president of Timtec , a supplier of hand-mades based in Delaware. For variety, hand-mades are better, he asserts, arguing that combichem libraries, limited by the number of viable transformations, rely heavily on analogues. "Combichem is good during lead development, when you've found a hit and want to explore around it. For finding the initial hit, however, it is better to use a wide variety of chemistries. But it depends on the target."

Timtec began as a broker for the Zelinsky Institute of Organic Chemistry in Russia, but now sources worldwide. "Our main difference from other companies is that we have a network of suppliers," says Mr. Niyazymbetov, 'Thore than 400 such research groups, labs and centers around the world, including the US, Canada, England, Germany, Egypt, India and China." TimTec's collection consists of high quality diversified molecules from in-house synthesis and various worldwide sources. Over 30,000 compounds are in-house and over 250,000 are available from overseas stock.

The company offers a variety of services to its customers and, indeed, established itself as a US business in 1995 to better offer those services--such as plating in 96 and 384 well plates, dissolution and plate replicating, custom weighing, barcode labeling, repackaging and organizing existing libraries--to customers in the US, where high throughput screening has been adopted much more quickly than elsewhere. TimTec provides not only chemical libraries for bioscreening, but also building blocks for combichem, database software, custom synthesis, plating, weighing, repackaging, labeling and quality control.

ChemBridge is another US-based player with Russian roots. The company entered the market as a latecomer in 1995, but it has quickly positioned itself as a leader with with a catalog of over 170,000 compounds and over 160 clients worldwide, including all major pharmaceutical and agrochemical companies, says Eugene Valsberg, president and CEO. A veteran of the pharmaceutical industry Mr. Vaisberg believed that diversity, quality and packaging were getting too little consideration from the suppliers of historical compound collections.

To address diversity, ChemBridge collaborated with the British company Chemical Design (since acquired by Oxford Molecular Group), in an application of 3-dimensional pharmacophoric base computational analysis techniques to select its screening library. "This was a very unique approach at the time," says Mr. Vaisberg. "Our product, the Diverset collection, brought tremendous success." To address quality, ChemBridge subjected all samples to 100 percent quality control; every sample goes through NMR, with the result that sometimes as many as 25 percent of a sourced collection is dropped. ChemBridge also brought packaging to industrial standards by introducing barcoding and sophisticated logistics. Compounds can be packaged in any desired solid or liquid form including 96 or 384 cell microplates. Of ChemBridge's 160 employees (soon 200), 60 are in packaging which uses barcode-based proprietary sample-tracking software.

Other important players in hand-mades include Bionet, ChemDiv (the US arm of Contact Services), ChemStar, Enamine, Interbioscreen, Labotest, Maybridge, and perhaps more than 50 others. The number of suppliers presents a problem, however. "Customers get confused," observes Mr. Niyazymbetov "and they are tired of working with so many suppliers." Consolidation is inevitable, he says, noting that Timtec itself recently merged with Molecular Design and Discovery (MDD), a small Canadian supplier.

A notable benefit offered by the suppliers of hand-made molecules is simpler, more flexible business models. "I can go to most suppliers I use and order anything from one compound to 100,000," Mr. Langley notes. "The library companies don't tend to work that way, they tend to tie in a big deal. There's nothing wrong with that, but that has been something we didn't want to get involved with, since we cover it in-house." He adds, however, that GlaxoWellcome's position is being reviewed and may change following its merger with SmithKline Beecham. "We are looking in more detail at these combinatorial chemistry companies because they are moving at a very fast pace."

The novelty of hand-mades can, after all, be an Achilles' heel. "With conventional synthesis, you can get a large number of very novel and diverse compounds, but they are more difficult to work with," Mr. Langley points out. "Which isn't to say that you can't--but one of the main drivers of combinatorial chemistry has been the perception that if you get a start, you can very quickly work around it, make analogs, study activity and go forward. That is a key advantage."

Additionally, combinatorial libraries, though they face synthetic constraints, present a more systematic screening collection. "When HTS became in vogue, there was an enormous demand for general screening libraries, and people would buy anything and everything they found," remarks Martin Stuart, vice president of business development at Tripos. "I'm not sure that's been terribly successful. We see a shift to a more informed strategy, where we look at targets and put together screening libraries that maximize our chances of success."

Tripos's own approach is an outgrowth of its 20 years' expertise in molecular modeling. "We found that there was a certain information base that could be used to design virtual libraries in silico, on the computer, which could be screened virtually using SARs [structure-activity relationships] that we'd derived using our computational techniques," says Mr. Stuart. Four years ago Tripos made its virtual library a physical reality. Called LeadQuest, it was designed to be drug-like and diverse. "That was the very first commercially available, designed library. It was a huge success for us, both strategically and financially."

Tripos integrates its LeadQuest library with a proprietary technology called ChemSpace to produce highly relevant, information-rich libraries that yield more efficient screening, says Mr. Stuart. Typically, a subset of the LeadQuest library is chosen in consideration of what is already known about the target and screened. On the basis of these initial results, Tripos uses ChemSpace to generate a virtual library of trillions of compounds in silico. Tripos then searches this library at a rate of billions of structures per second using descriptors that correlate with

activity to identify a new library--accessible by combinatorial chemistry--for further lead optimization.

Arena Pharmaceuticals, for example, had a 5HT 2A/2C target for schizophrenia. Tripos used a shape descriptor extracted from initial screening results to generate additional libraries for more refined screening. "In this collaboration with Arena, we were able to go from the very beginning of the project to a highly active compound with demonstrated in vivo activity in nine months," says Mr. Stuart. He notes that Arena is now seeking to partner that preclinical candidate.

When combinatorial libraries first appeared, they were severely limited by the range of transformations available to combichem companies, but their toolboxes have gained considerable heft, say participants.

"Five years ago, combinatorial chemistry was driven by what was feasible; now we are much more able to say at the start what we would like to make, and then to make it in a high-throughput fashion," says Steven Hill, CEO and president of ArQule, based in Woburn, Mass. ArQule has spent 7 years developing a set of 200 transformations that can be automated and performed at high throughput in the solution phase, and the company is expanding its repertoire to include solid phase chemistry. "It's not trivial to take a reaction from the bench to a high throughput robot," Mr. Hill stresses. "That's one of the values we create."

Drawing on these chemistries, ArQule generates 200,000 compounds per year for its Mapping Array Libraries. Of these, a subset of 12.5 percent, or 25,000, is chosen by computational methods to achieve the same diversity with fewer analogs. When hits are obtained from this subset, which is called a Compass Array Library, analogs that have an improved affinity for the target are extracted from the Mapping Array. Further refinements may be obtained using a Custom Array Program in which compounds are synthesized combinatorially on an exclusive basis for individual collaborators.

ArQule's approach--what it calls its AMAP (automated molecular assembly plant) chemistry operating system--has been extremely successful, to judge from two deals cut with Pfizer and Bayer in 1999. For a possible total of $117 million, Pfizer has engaged ArQule for a 4.5-year collaboration that will eventually lead to the transfer of the AMAP technology to Pfizer. Bayer for $30 million, has entered into a three-year collaboration with ArQule to generate libraries of several hundred thousand compounds for Bayer's exclusive use. These deals show that ArQule has a strong position in the combichem services area, says Mr. Hill. "But I hesitate to use that term," he notes, "because our real goal is to apply our technology to drug discovery programs--to bring our chemistry together with targets from target-rich genomics/biology companies and do drug discovery programs leading to INDs [initial new drug applications]."

Coelacanth, based in Princeton, N.J., has made chemistry central to its identity, as well, but it differentiates itself in two ways. One is the company's synthetic approach, ClickChem, which owes its name to K. Barry Sharpless, one of Coelacanth's founders and a professor of

chemistry at the Scripp's Institute. Prof. Sharpless uses the term "click chemistry" to represent a suite of synthetic reactions that are so versatile and efficient that they practically "click" molecules together says Alan Main, president and CEO.

Instead of applying this set of transformations to standard building blocks obtained from commercial suppliers, Coelacanth manufactures its own set of "pharmacophoric," or druglike, building blocks, which have been identified as recurring elements of successful drugs. "Our hypothesis is that these structural elements are fundamentally not very toxic, aren't highly metabolized and interact favorably with proteins," says Mr. Main. "That is why they show up in many different types of drugs. For example, indanes appear in opiates, anti-inflammatory and blood-pressure lowering drugs."

Drawing on its collection of 1,500 pharmacophoric building blocks, Coelacanth synthesizes a completely new library every 4 months, each designed with a different theme. One library focused on heterocycles, another on enzyme targets. A series currently in design will apply Sharpless chemistry to the over 200 optically active terpenes found globally to make a library with natural-product characteristics. "That's a lot of diversity," says Mr. Main, "which is what companies are looking for--things their own chemists haven't come up with."

Mr. Main expects chemical expertise to increase in value as the backlog of genomic data builds. "I think everyone has realized that all this gene sequencing data has incredible potential, but someone has to take that information and turn it into value. Just as in the Internet industry there are essential infrastructure companies, we consider ourselves a key part of the genomics infrastructure necessary to convert genomics data into drugs."

David Snitman, chief operating officer and vice president of business development at Array BioPharma, offers a similar perspective: "Our focus as a company is to look at creating innovations in chemistry to meet the challenges brought on by the huge investment in biology that has taken place over the last 5 or 10 years." He and like-minded chemists who had made their way to Amgen after years in big pharma saw a mismatch in the advances of genomics and the practice of chemistry, which was still slugging it out as it had been for many years.

One reason for the situation was the mediocre quality of the starting materials. "They were not being made to do SAR elaboration around core structures--they were simply petroleum by-products or compounds used as intermediates in some past drug," says Mr. Snitman. Improving the quality of these starting materials became Array's Optimer building block strategy. "However," he adds, "we realized also that the quality of the lead that you optimize depends on the quality of the library that your lead is coming from." Array therefore set out to create libraries based on knowledge of past targets as well as core structures that have repeatedly had activity with targets such as G-protein coupled receptors, enzymes such as kinases and proteases, and nuclear receptors, with a special emphasis on protein-protein interaction.

The resulting quality leads, which can be easily followed up, will dramatically streamline the

discovery process, says Mr. Snitman. "For example, if you screen a random library and have great initial activity from a natural product, it might take 10 chemists 6 months just to evaluate whether you have something worth pursuing. That's the point where a lot of chemistry goes and where the timeframe can be shortened. If you have multiple hits that can all be optimized in an automated format with quality building blocks, you can keep the process in automation longer. That will not only speed up the process; we think you'll have higher quality drugs going into the clinic with a higher survival rate and a better chance of being a blockbuster."

These and other refinements add up to higher quality, a trend driven by a more demanding customer base, notes ChemBridge's Mr. Vaisberg. "Ten years ago, there was so much hype in combichem that unreasonable amounts of money were paid for pretty poor compounds," he says. "The big deals with milestones and royalties are gone. In combichem only vendors who can provide small libraries with diversity, complex chemistry, purity and 100 percent quality control will survive." Mr. Vaisberg points to ChemBridge's own in-house combichem effort, with a staff of 90. Its first product, the Pharmacore library, was introduced one year ago. It is founded on a large collection of proprietary building blocks.

GlaxoWellcome's Mr. Langley sees no sign that the stream of new structures crossing his desk will slow anytime soon. "If anything, it's still growing, even for compounds produced by conventional synthesis," he says. Demand will keep up with supply, he predicts. "The simple fact is that none of us have all the answers on our shelves. We've got to go outside looking for compounds. These companies won't all survive--there must be a finite limit to how many deals are out there. But I don't see any immediate rationalizing. For the next five years at least, there is scope for most of the compound suppliers and library companies."

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Issue: August 21, 2000