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Not by drug development alone

Bayer's Dr. David Naveh believes the key to Israeli biotech's long-term survival is a biopharmaceutical manufacturing and services facility.

Nir Nathan, Los Angeles 21 Aug 02 12:15

The future of Israeli biotechnology does not just lie in developing revolutionary pharmaceuticals, foreign investment or state funding for start-ups. The key to long-term survival and development is a biopharmaceutical manufacturing and services facility.

At least that's the opinion of Bayer Biological/Biotechnology Worldwide CTO Dr. David Naveh. From his Silicon Valley office, Naveh stands behind the initiative to establish just such a facility in Israel, confidently asserting that the industry's future will rise or fall on the facility.

"This facility will be able to conduct clinical trials, speed the industry's maturity and help found built-to-last companies with market values in the hundreds of millions of dollars. The facility's main contribution will be in raising the valuations of Israeli companies.

Naveh says Israel's biotechnology industry is like one big pharmaceutical company that conducts a lot of basic research but lacks development muscle. Young and old companies in the sector need high quality material for human clinical trials. This material must be created at the facility using Good Management Practices (GMP) standards.

In the absence of such a facility in Israel, young companies competing for these services are forced to sell technology, thereby losing their most important asset. The lack of such a facility in Israel forces many companies to pay up to 90% royalties for development cooperation instead of marketing cooperation. In other words, the company retains only 10% of future sales. These deals, which have high potential value (assuming the drugs work, of course) end up yielding only a low a dollar advance.

The proposed facility is intended to provide an equitable solution to this problem, restore investment and even yield a 50% profit. There are two problems, however: a \$100 million price tag, and an estimated six years to build and raise the values of its participating companies.

Where will the financing come from? Naveh claims there is no relationship between the project being worthwhile to the individual investor and the advantages it will bring to the Israeli economy. "I simply don't believe that private parties will finance a facility of this kind," he says, categorically declaring, "Contract manufacturing in which the profit is 50%, while high-tech investors expect a higher return. The facility will be profitable, and won't need subsidies. There is little risk to the 50% profit, since it does not depend on the isolated success of a single company."

"Globes": If that's the case, why won't venture capital funds invest in it?

Naveh: "The life span of the average fund is 8-10 years. If a fund says the idea is marvelous, it must take into account the three years that it will take to finish the facility. Only then will Israeli companies take up residence there, and their valuations won't rise for another three years. Their exit timetable is not suitable for a venture capital fund. That's why we're calling it infrastructure. Not every profitable project is suitable for a fund."

What about ventures with established corporations, even Israeli ones like Clal or Teva (Nasdaq: TEVA)? Why wouldn't they invest in infrastructure that would give them rights?

"They also can't wait. I'm not solving an immediate existing problem. Let's assume I now have a product and I need manufacturing capacity. I have a budget and I'm willing to pay an average of \$2 million a month for GMP standard manufacturing capacity at a good facility. Strategic investment is reserved for new technologies, not for spending on somebody else's infrastructure."

So you recommend state financing? With all its bureaucracy?

"That's not the point. The facility is the kind of project that will generate immense advantages for Israel's

biotechnology industry. It will not solve company X's current problems.

"The US and Europe have an entire contract manufacturing industry, but their industry is mature with immediate needs that must be met. There is currently a huge shortage of such facilities that will last for the next decade. Israel has no such mature industry, so it would be unnatural to build it without some form of impetus, unless it's called a national infrastructure project.

"In Singapore, the government invested \$5 billion in biotechnology, even though the country lacks a life sciences infrastructure like Israel's. Even Cuba invests hundreds of millions of dollars in this. Such investments include manufacturing facilities, but these countries lack the trained manpower with accumulated industrial experience. Their model is institutional, while the suitable model for Israel is individual, once the facility is built."

When would the facility become independent and profitable, and begin giving the state a return on its investment?

"Based on our model, \$60 million would be invested in construction, and another \$40 million in start-up costs and maintenance until the break even point is reached. It would become profitable in its third year. The plant would be entirely private, and its employees would have shares in the companies that will be the plant's customers. We're still working on the financial aspects, but there'll be enough money to give the state a return on its investment within a few years. Under the model, the property itself might be state-owned. Obviously, the project's team cannot be members of a state-run institutionalized plant, but must be veteran Israeli biotechnology industrialists."

Is outsourcing a solution for Israeli companies?

"No, because there's no learning curve. I mean that the human infrastructure for process development, formulation and trained production and management staff are not created. A company that outsources does not develop experienced production staff, but pays someone else. It usually doesn't succeed on the first try, and the money runs out by the second or third try. The result is that the company is forced to sign licensing agreements for its projects with a large company at a low price, even if the outsourcing succeeds.

"In biotechnology, the company is production. Companies like Genentech (Nasdaq:DNA) have 4,200 employees, of whom 3,000 are manufacturing staff. This is also why US companies insist on preserving their production rights in deals, even if the drug fails in later development stages. The development-manufacturing infrastructure remains and can be used for other products."

Do you think your model will create another Israeli pharmaceutical giant?

"There is no deterministic method that can guarantee an Israeli bio-Nokia. The goal is to create long-term companies with sufficient capital, mass and ability to survive market swings, and even acquire technology. One or two of them will even achieve market values of \$500 million or more, changing the Israeli biotechnology scene from dozens of boutiques to a normal distribution of early stage and mature companies. The facility will help Israeli companies reach the second and third stage, and even launch drugs."

How will this be seen in valuations?

"The valuation of companies with a successful second stage product begins at \$50 million, and can reach \$200 million by the end of the process. In the third stage, prior to launch, it can reach \$600 million, and much more later on. With a second stage market value of \$200 million, you can do a lot of things, and there is no need to beg constantly."

And is that good for the Jews?

"We calculated that if there were 20 customers in the first three years, half of whom had valuations of \$20-200 million, the total size would be \$1.8 billion. Even if the increase is only five-fold, the increase in their market value is almost \$1 billion, naturally assuming it is possible to reach the clinical trials stage. And its all based on an initial \$100 million investment. After two and a half years, the facility will have enough customers to finance its operating expenses."

As mentioned above, Naveh currently works for German pharmaceutical giant Bayer (NYSE:BAY; XETRA:BAYG; LSE:BAY). Naveh began his career at the Technion – Israel Institute of Technology's molecular

labs, studying biotechnology and food engineering. He received his Ph.D. in biochemistry from the University of Minnesota, and was a professor at University of Wisconsin, Madison.

Naveh also worked as a project manager developing Interferon at Schering-Plough (NYSE:SGP), was COO at Centocor, for whom he established the world's largest antibodies production plant in Europe in the 1990s. Naveh says Centocor made a \$500 million mistake in developing a drug for the septic market, after which it was acquired by Johnson & Johnson (NYSE:JNJ). The company is now flourishing.

A decade ago, Bayer, which until then developed plasma products, decided to enter biotechnology. However, opposition at the time by Germany Green Party to biotechnology research, alleging genetic mutations, contamination and the like, forced the company to change its strategy of entering the biotech niche.

Bayer decided to convert Cutter Labs, a plasma products company acquired in 1978, into a genetic products developer. One of its products is Factor 8, the most complex and expensive protein in the world, used to treat hemophilia and costing \$5.5 million a gram. Factor 8 sales currently total an estimated \$3 billion a year, and are expected to reach at least \$5 billion by 2010.

Bayer also invested in a strategic partnership with Israeli start-up Omri to develop a treatment that would reduce Factor 8 injections from every other day to once a week. Naveh relates that the Bayer-Omri contract stipulated that Omri would be the exclusive manufacturers, and would not transfer production to Bayer.

"We're now investing in another Israeli company," adds Naveh. Naveh is also responsible for establishing a \$300 million biotechnology infrastructure in Germany, although the project has been suspended, due to consolidation considerations in the sector.

Naveh, it must be said, is rather unenthusiastic about the Israeli dream to bring large pharmaceutical companies to set up R&D centers in the country. He believes the companies would prefer to send scouting parties to hunt Israeli technology.

"Israeli technologies have already helped build successful companies like Serono (NYSE:SRA: XETRA:SEOZ). The strong encouragement by government offices and venture capital funds seeking an early exit results in corporate colonialism, buying up Israeli technology. The result is a negative feedback cycle in which start-ups make premature exits, licensing or outsourcing agreements, and fail to reach a critical mass.

"In some cases, in order to survive, they must find new technologies that are then sold too soon. Unlike the high-tech industry, pharmaceutical development takes 10-12 years, and costs \$500-800 million. Consequently, pharmaceutical companies want to have their finger on the pulse of development, carrying it out in their headquarters.

"In high-tech, an advanced chip take three years and \$50 million to develop. In this case, it's worthwhile for companies to transfer early-stage development to a location where development is effective. The pharmaceutical industry strongly centralizes control of development, and the current trend is for consolidation, due to the immense inherent costs and risks of drug development."

Naveh also warns about a reality that many people might not be aware of. "Academe does not have enough ideas to light the fire and constantly maintain hundreds of companies. We're already exploiting the science developed over decades. Israel's biotechnology industry is rich in preliminary ideas that don't pass muster. It's important to understand that in the post-genome era, the genome bubble companies discovered many molecules with *in silico* properties, but they are valueless, because of the development bottleneck, i.e. materials for clinical trials and clinical results."

Naveh tells about a deal Bayer signed with CuraGen (Nasdaq:CRGN), under which CuraGen paid Bayer \$400 million to test a large number of molecules, i.e. active genes. "If some of them really worked, they'd get a percentage of the sales," says Naveh.

While Naveh initiated the Israeli biotechnology facility, he has been joined by some of the leading names in Israeli and global biotechnology, including Clal Biotechnology Industries CTO Avri Havron, [Polyheal](#) CEO Dr. Menachem (Mendi) Ze'evi, and Biogen (Nasdaq:BGEN) executive VP R&D Dr. Burt Adelman. The group operates under the aegis of [US-Israel Science and Technology Commission](#). USISTC and the Office of the Chief Scientist.

With such a group, what has to happen for the project to get the government to pay attention?

"The Ministry of Industry and Trade has to realize that Israeli biotechnology will not develop and will have no future unless companies are able to achieve valuations of hundreds of millions of dollars. It would be a naïve capitalist who imagines that any project that cannot raise private capital has no economic advantage. The fact that Bayer or Teva won't invest in the project does not mean it's not worthwhile."

Who's already supporting the project?

"Former Merck & Co. (NYSE:MRK) senior VP Barry Cohen, who is a member of Teva's board of directors, convinced me such a project had a chance. He reminded me that Sweden and Denmark, which have similar populations to Israel's, have major pharmaceutical companies: Pharmacia (NYSE; XETRA; Stockholm:PHA) and Novo Nordisk (NYSE; XETRA; Copenhagen:NVO; LSE:NNO). Applied Materials (Nadaq:AMAT) president Dan Maydan is a great believer in commercialization, and he convinced me that the solution was not founding integrative companies, but companies that can survive on their own. Most people say it won't happen, and we're daydreaming. I think that the right vision, persistence and stubbornness are needed to get a project of this kind up and running."

There is also political reality.

"Israelis believe it is better to take \$100 million from the budget and disperse it among a lot of small projects. Our group thinks this is a mistake. Small projects with government and venture capital support that increase their value tenfold and are sold don't enrich the whole country or build an employment infrastructure and other side benefits. They merely enrich a few individuals.

"A \$100 million investment is indirect support in a group of select biotechnology companies that have a chance of commercializing, rather than gambling on a particular technology."

\$100 million is still \$100 million, and in times like these...

"I know. Some of what I've said is naïve. I spoke with Ministry of Industry and Trade director general Amir Hayek, and he told me something on the lines 'Do you think anyone at the political level will put up \$100 million? We're dealing with urgent matters of existence.'

"Nevertheless, I hope and believe there will be support from biotechnology industrialists, high-tech people and economists for the facility. It's important to understand that we're just starting on a 20-year biotechnology revolution, and Israel has only one chance to participate."

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