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VORTICAL FLOW

Nasal Delivery's New Direction

IN THIS ISSUE

INTERVIEW WITH HOVIONE'S CEO
MR. GUY VILLAX

The science & business of specialty pharma, biotechnology, and drug delivery

Ms. Emily K. Pauli
Modeling & Simulation for Drug Delivery: Accuracy, Speed & Flexibility

Mr. Marc Giroux
Controlled Particle Dispersion™: Applying Vortical Flow to Optimize Nasal Drug Deposition

Matthew D. Burke, PhD
Drug Delivery Technology Assessment: The Eight Assessment Gates

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Drug Delivery EXECUTIVE

Hovione: More Than Just Very Good Small-Molecule Chemistry

MR. GUY VILLAX
CEO, HOVIONE

"Many of the new compounds in development present significant challenges. For example, they may be very fragile, and in simple terms, galenic techniques enable the chemist to isolate the API already in a preformulated more stable form. We call these Enhanced APIs."

There is much talk about the convergence of disciplines in the life-sciences area. Hovione has been involved in manufacturing APIs under current cGMP for nearly 50 years. Many development candidates present an increasing set of challenges: complexity of the molecule, poor bioavailability yet highly potent, very high purity, poor stability, etc.....often simultaneously. Meeting these demands has opened opportunities for the "top-of-the-line" Contract Manufacturing Organizations to develop strengths in new disciplines and to combine capabilities never before found on the same campus, let alone within a validated commercial scale GMP environment. Hovione has traditionally been a CMO of small molecules and is now adding new skills and capabilities that address the special needs of large molecules, peptides, and antibodies. Hence, Hovione now offers a range of galenic enhancements that contribute decisively to making certain APIs into viable industrial propositions, in purpose-designed containment areas built to uncommon standards, to serve projects managed with multidisciplinary staff. Drug Delivery Technology recently interviewed Mr. Guy Villax, Hovione's CEO, to discuss his company's philosophy and business strategy, a vision based on an intimate understanding of client needs and technology trends. APIs of the 21st century present increased difficulties not only in their traditional fields (chemistry, engineering, analytical chemistry), but in new areas of technology as well as management.

Q: Hovione is traditionally known for its APIs, and you are now offering formulation services. Can you tell us about your business?

A: Hovione has been manufacturing APIs by chemical synthesis for over 40 years. Today, we operate two large FDA-inspected plants and a technology center, respectively in Portugal, Macau, and New Jersey. We employ 630 staff, with 125 dedicated to process chemistry R&D. We manufacture routinely 17 commercial compounds and are involved in several dozen development projects for which we produce GMP quantities of APIs for clinical trials. All the processes are either invented or developed in house. Intermediates are not our business, the products Hovione sells are final APIs used for oral, topical, injectable, or inhaled administration. This API mindset differentiates us from the competition that is often mostly focused on intermediates (the large pharma's tax strategies have blinkered most of the outsourcing fine chemicals industry to ignore the galenic needs that are paramount downstream). At Hovione, that is not the case. We have been aware of polymorph issues, particle size distribution, flowability, density and compressibility, electrostatic charges, VOC content, etc for a long time. In addition to control of chemical attributes, Hovione has decades of experience with the products' physical attributes as well as with microbial contamination considerations.

The only area in which Hovione has formulation tradition and a very considerable amount of know-how is in dry-powder inhalation. This developed because of FlowCaps®, our patented DPI, which is a very simple, capsule-based, inexpensive device. FlowCaps® is available for licensing for specific APIs in specific markets, and the first commercial launch is expected in 2005. The licensee is to a billion-dollar generic medicines company. What is new in terms of formulation services is the success of our Particle Design Technologies initiative. We have been

promoting our services and know-how surrounding the control of the physical attributes of the API from milling and jet-milling to careful control of the crystalization process, making use of ultrasound or supercritical fluids. We have also invested in spray-drying to address the needs of very specific APIs or specialized excipients, such as Cydex's well-known modified cyclodextrine Captisol®. As we were offering these services to the API market, we noticed that there was as much interest in our work by pharmacists as there was from chemists. It became very clear that this Chemical/Galenical interface point is a tremendous source of solutions and cost reduction and that it has been traditionally ignored. Many of the new compounds in development present significant challenges. For example, they may be very fragile, and in simple terms, galenic techniques enable the chemist to isolate the API already in a preformulated more stable form. We call these Enhanced APIs.

Q: Why have pharmacists and chemists not worked this out before?

A: I think many have tried. I recently discussed this with a senior industry executive who told me this had been tried at Roche 8 years ago but that the silo organization of primary and secondary production made any coordination very difficult. On the other hand, it does seem that when margins are tighter and volumes are very large, this cooperation occurs more frequently and successfully. For instance, at Roche Vitamins (now a DSM business), very sophisticated formulation techniques were already integrated into the API batch record in the closing stages years ago. What surprised him was to see this initiative coming out of a fine chemicals company.

Q: So how did this Chemical/Galenic interface come about at Hovione?

A: I think Hovione has traditionally approached every problem with a multidisciplinary "can do" attitude. We view ourselves as generalists keen to embrace difficulty. We don´t shy away from a technical challenge, and people at Hovione are curious to discover and eager to learn, they do "whatever it takes." So when challenges arise, we never hesitate. Over 30 years ago we were doing reactions at -50º C and high-pressure hydrogenations with our own homogenous catalysts, and 10 years ago, we were doing chemical reactions and API isolation in clean rooms, or installing the first industrial-scale gaseous phase permeation unit in Europe. As such, whenever an opportunity arises for us to get into new fields, we're there whether it's ultra-filtration, supercritical gases, purification with resins or with pressure chromatography, spray-drying, freeze-drying, etc. This "can do" approach that characterizes us is also present in doing things for customers flexibly and quickly whether its reconfiguring a plant overnight or installing new equipment and putting it into operation in a month or two. Again, getting into spray-drying resulted from being keen to meet a customer's requirement.

Q: Do customers come to you because you are low-cost or because you offer something they cannot get elsewhere?

A: I believe more than anything that Hovione customers get extremely high value for the money they spend. We may be more expensive than most, but the customer gets better and more reliable solutions quicker. They get a validatable, robust, truly industrial process worked out with the best possible supply-chain solution. Our 40-year-old expertise in strategic sourcing integrates process research to develop a process that combines low-cost products from reliable China suppliers with well-controlled independent chemistry. Biotechs or development-stage companies get the most value from Hovione because we take responsibility for 100% of the areas related to the API. Furthermore, with our extensive track record, we can provide much input and reference points for regulatory strategy or patent approaches. For instance, in the list of 19 compounds that Goldman Sachs expects to see approved by the FDA and launched in the US in 2005 with sales of more than $200 million, Hovione is involved in the API of 3 of them.

Q: Can you provide any examples?

A: Sure. What Hovione did for Agouron's Viracept is well known to the public. This was a 31-day cycle-time product (the compound had 5 chiral centers). From signing a term sheet, in 8 months, we made the bio-batches for stability and filing, we re-engineered and programmed the automation for a 150m3 plant, we validated the process at a 500-kg batch scale (a fourfold increase), started producing 4 tons per month, and completed successfully a PAI inspection. The high volumes led us quickly up the learning curve, and we improved yields and cycle time very significantly to such an extent that after 3 years of production, raw material cost was reduced by 70%. Unfortunately, Agouron was taken over by a Big Pharma giant with sufficient manufacturing capacity.

Another recent example was a company that needed its API spray-dried with an excipient to make a chewable tablet. They came to us because their CMO partner had decided to stop providing the service, and they were 1 year away from filing. Within 4 months, we transferred the process and the analytical methods, we scaled-up the process to double the throughput, and we validated the process successfully. We ensured the NDA filing date remained unaffected despite the change of primary manufacturer.

Using spray-drying to isolate compounds has also been a great surprise to many of our customers. They usually start by shying away from the technology because they perceive it as not available at large scale, but when they hear that we have validated pharma-grade industrial-scale equipments and have the know-how to come up with lab-scale proof-of-concept in weeks, they are quickly converted.

Q: What has the New Jersey Technology Transfer Centre done for you?

A: More than anything else, in 2 years of operation, it has put our name solidly on the US map. It confirmed Hovione's 100% commitment to the US market and to serving the Biotech sector. We now have almost 30 staff, and that unit already sells more per US employee than the Group's average but more significantly, the TTC has already successfully transferred two projects to our plants. In two separate instances, projects developed in New Jersey and used to make clinical material in New Jersey progressed so well in the clinic that additional material was needed. This exceeded the TTC's capacity, so one drug went to Macau, the other to Portugal. The TTC is a source of great pride to us. We started with a cornfield and 18 months later, we had a facility that every visitor compliments us on. We have hired some very seasoned US scientists; many came to us because they wanted a change from Big Pharma. They have an extraordinary amount of know-how and depth of knowledge, and in addition, they do an excellent job at mentoring and developing the young people we send from Portugal and Macau to the TTC for short spells for training and customer contact.

Q: Can you discuss your generics business since we have mostly discussed your innovator business?

A: Hovione gives equal importance to both segments: serving exclusively the needs of innovators as well as the generics industry. We develop APIs for which patents are about to expire and offer them to the market, but also work on special projects on an exclusive basis with specific generics firms. Many of the larger generics houses do not have chemistry capabilities, and they come to us when they need product development strategies that demand chemistry expertise or other special technical capabilities. In other words, Hovione is keener to work on riskier, more value-adding, and service-intensive challenges than commodity-like activities. Making APIs for inhalation is a case in point. Our expertise in this kind of formulation allied to our profound know-how in particle design has made us uniquely qualified to provide client-specific grades of fluticasone for topical, nasal, or dry-powder inhalers.

Q: Hovione has been in the news a lot lately regarding an important issue, can you tell us more?

A: Recently, there has been much coverage of the lobbying Chris Oldenhof of APIC and Peter Nagler of EFCG have started with a view to implementing a European equivalent to the FDA's Foreign Inspection Service. I was little more than a catalyst and gave a face to the issue. This has received great support, and one comment that came from America read, "I have now seen your face in several prominent trade journals saying exactly what needs to be said and done in support of the European API manufacturers." Heads of family businesses are lucky in that they are allowed the latitude to speak their mind, but again, they also have a duty to do what they think is right, rather than just what is profitable.

Q: Hovione seems to be growing steadily, what are your future growth strategies?

A: Our hard work does yield results. Our sales were $65 million in 2002, $75 million in 2003, and this year, they will be $81 million. Unfortunately, when converted into Euros, the numbers indicate somewhat of a stagnating performance around 65 million, which means that with a majority of our operations located in the Euro zone, we are suffering from the Dollar weakness, which is frustrating. But we did have it pretty good a few years back. Most of our agreements are long-term, and our partners usually welcome exchange-rate clauses in which we share equally the currency fluctuations. When we have a good year, our EBITDA is usually in excess of 30%, when its bad, it is around 25%.

Growth for us has always been internally generated. We are far more focused on training our staff and motivating them on designing flexible plants that will serve us for decades to come and on investing in know-how, rather than buying up other firms or getting listed in a stock market. Making APIs, enhancing APIs, and serving pharma firms is not exactly straightforward, so the less distractions the better. Worrying about the stock price, linking compensation to financial targets, etc will never be the best way to serve customers – and that is what matters, which is why we focus on having a great team with the best resources. ♦