Marc-Olivier Geinoz â?? CEO, Dipharma SA

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03.03.2021

Tags:

Switzerland, Dipharma, Rare Diseases, Generics, CDMO, CMO, Manufacturing

Dipharma SA is a Swiss specialty pharmaceutical company, developing improved generics medicines for rare metabolic diseases. Founder & CEO Marc-Olivier Geinoz discusses why the company has chosen to compete in the largely unexplored rare diseases generics space, its direct presence in the German market, and the opportunities inherent in metabolic disease small-molecules.

Can you introduce the company and its current focus?

Dipharma SA is a Swiss-based company which provides high-quality drugs with improved properties, such as for example an enhanced stability, to those who suffer from congenital metabolic disorders.

You have been involved with your familyâ??s CDMO business for many years, but decided to start a new venture. What motivated you to do so?

Our group of companies was born of innovation. My grandfather, Dr Mario Biazzi, was a chemical engineer and inventor: he made several contributions in the field of explosives, including the first continuous and safe process to manufacture nitroglycerin. Throughout our history, innovation has

always been at our core. In the group, we have patents or patent applications covering more than 250 inventions. We like new technologies and striving to find solutions to complex challenges.

As far as the pharmaceutical industry goes, we have a very unconventional history. After starting his engineering firm in 1936, my grandfather thought that, in order to stay at the leading edge of designing and building equipment to manufacture civil explosives, it would be good to actually operate a plant and experience on the field what could be further improved. For that reason, he started a company named Dinamite SpA, located in the Udine province, some 100 km north-east of Venice, Italy.

Unsurprisingly, Dinamite SpA was manufacturing dynamite, a civil explosive made using nitroglycerin as its active substance. The company was therefore manufacturing large volumes of nitroglycerin, using my grandfatherâ??s invention. This is how, without a particular intent to be involved with medicines, we started to receive requests for pharmaceutical-grade nitroglycerin as an API to treat angina-pectoris. The company developed into GMP manufacturing and changed its name to Dinamite-Dipharma SpA. Later, it abandoned the field of civil explosives and its name became Dipharma Francis Srl. Today, Dipharma Francis Srl is a CDMO operating with four cGMP manufacturing sites located in Italy and USA. It excels at handling complex chemical processes safely.

As I was leading our CDMO business, I realized that more and more low volume molecules were being introduced, and a large share of new approvals were related to orphan products. With our long-time experience in dealing with the merchant market for generic APIs, it was clear that orphan drugs were not well suited for the suppliers of bulk active ingredients, hence the idea to start an entirely new business with focus on the drug product. After all, it was not the first time in our history that we moved into an entirely new, yet somewhat related, field.

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What is the reasoning behind the companyâ??s current focus on small-molecule generics for metabolic rare diseases?

As you know, the Orphan Regulation entered into force in the EU in the year 2000. As such, the first orphan drugs were starting to lose orphan drug exclusivity around ten years ago. Nonetheless, there was practically no generics competition due to the fact that developing a generic of an orphan drug costs as much, if not more, as developing a generic of a blockbuster drug, but with low volumes spread over a market that is geographically very fragmented.

On the other hand, the orphan drug legislation had a very positive effect in fueling research on rare diseases. Indeed, this is witnessed by the high proportion of orphan drugs that have been approved in the past few years. Growth on orphan drugs has been strong, and now orphan drugs represent circa 15 percent of global pharmaceutical prescription spending. This growth trend is likely to continue as it is estimated that there are roughly 7,000 rare diseases, and the majority of these still have no approved treatment.

From this perspective, rare diseases are only rare when taken in isolation; together there are many of them, and whilst the number of people suffering from each individual disease is very small (typically less than five out of every 10,000 people), with roughly 7,000 of these diseases in existence, it is estimated that perhaps around seven percent of the global population could be

affected by a rare disease.

In Switzerland, the number of patients affected by rare diseases is estimated to be more than half a million. This is more than the number of people with diabetes (four percent of the Swiss population).

For some ultra-rare genetic diseases, the annual treatment cost may exceed USD 100,000 for life. In some cases, payers are reluctant to cover the treatment costs. Indeed, many studies have shown that orphan drugs currently have more coverage restrictions than non-orphan drugs.

Considering the combined prevalence of rare diseases and the introduction of new therapies for unmet medical needs, it is little wonder that the spending on rare diseases will continue to increase over the years. Without generics competition to curb the increase in costs, there is a strong risk that the issue of coverage restrictions might worsen, and with it the inequality of coverage between countries and diseases.

Even though the profitability of developing generics for rare disease is very much questionable, we believe that there is a strong need for cheaper alternatives.

And why the focus on small-molecule generics for metabolic rare diseases?

The focus on small molecules was an easy decision: thatâ??s a field our group of companies is comfortable with. As a group of companies, we have been making small molecule APIs for decades, serving customers all around the world, in particular for USA, EU, and Japan.

The choice of metabolic rare diseases was one of circumstance. In terms of revenues, the largest therapeutic class in orphan drugs is oncology. The second largest is metabolic diseases. Since the technologies available at our CDMO business were more suitable for molecules in the field of metabolic diseases, it was easier to trust a sister company for our supplies rather than a third party.

We do not rule out that at some point in the future we will expand into other fields. But right now, we believe there is still a lot to do with our current focus, and we therefore prefer to strengthen our company in that specific area.

Which are the main challenges a pharma company faces when targeting rare diseases in Switzerland?

As the Swiss market is small, companies do not always register their orphan products with the authorities. Instead, they opt for a special license scheme where the product is imported from another country where it has been registered. This is more expensive and more time consuming for both patients and physicians. It also means that there is no reference product registered in Switzerland, hence hindering the regulatory registration for generics.

It was a lose-lose game and the Swiss authorities have addressed the issue: in order to stimulate pharmaceutical companies to register their orphan products in Switzerland, the regulatory authority Swissmedic recently implemented a new procedure to grant orphan drug status (ODS) to medicinal products treating conditions affecting no more than five out of 10,000 people in Switzerland, or that have been granted ODS in another country with equivalent medicinal product control.

The procedure with prior notification has been used for the recognition of ODS since 1 August 2019. The advantage for the pharmaceutical companies is twofold: on one side ODS benefits from an accelerated approval procedure, on the other the approved medicines will benefit from a data exclusivity period of 15 years, meaning that generic equivalents cannot be approved during this period. For the patients and physicians, this should also ease the process to procure the product and obtain reimbursement from the insurance companies.

From what you describe, it seems the Swiss market is not particularly attractive for a company like yours, offering generics for rare diseases. So why did you establish the company in Switzerland?

As a target market, you are right. Switzerland might not be, as for now, a very attractive market: the market is small, and 15 years of orphan exclusivity is a lot. But Switzerland is a fantastic place to attract talented employees in the field of life sciences. It also enjoys mutual recognition of GMP with many countries, and Swissmedic maintains a close relationship with EMA and FDA. Switzerland is a business-friendly place with a strong work ethics, as well as a stable and rather predictable environment, which suits our long-term investments well. Also, it has a good reputation for innovation and quality, two aspects that are very important for our business model.

Last but not least, it is my home country where I have grown up, and even though my grandfather was an immigrant, the family has always felt â??at homeâ?• in Switzerland.

What is the companyâ??s current strategy in the rare disease generics market?

Ideally, we want to be the first generic in the market, always offering a product of superior quality, with an improved offering wherever possible. We are also targeting as many countries as possible with each of our products.

What is your current commercial model?

We use partners for commercialization except in one market, Germany, where we have decided to build a direct presence. Unfortunately, we started in Germany just before the pandemic and it has not been easy to develop the business as fast as we had hoped due to the restrictions in place, such as the non-acceptance of in-person visits to doctors.

In most other countries, our revenues would not justify hiring the personnel needed to do a good job, and therefore it is better to keep our costs variable by relying on partners. In some countries, a direct presence could be economically justified, but we are a small company and do not want to stretch our resources too much. Rather, we focus on developing great quality products and leave commercialization to our partners around the globe.

What are the main obstacles you are facing with that strategy; how do you convince patients and payers?

First of all, generic substitution for chronic rare diseases is very slow. Orphan drugs are not a priority for substitution with many payers, who place far more emphasis on their big expense volume

products. This, unfortunately, plays against the interest of ultra-rare disease patients because the payers tend to reimburse products for few indications at originator price, rather than many indications at generic price.

Furthermore, even in countries where a tender is mandatory once a generic product is available, winning the tender does not always guarantee that the generic switch will happen.

Another issue is that there is a psychological barrier for patients (or their families) to substitute a drug that they have been using for their entire lives. Imagine a family that has been using a product for ten years and, suddenly, the payer tells them that they must switch to a cheaper drug; they might feel that their child is not a priority, and that the substitution product is of cheaper quality.

That is why quality has always ranked on top of our values. We strive to offer a superior quality, such as for example a superior purity. Purity is important because when you take a product for life, who knows how much and what impurities might accumulate in your body and their effect in the long run.

How do you see Dipharma evolving in the near future?

We are expanding our portfolio and will launch more products. We are also consolidating our presence in Europe and expanding to new territories: we already have registrations pending in a large number of markets where our products have not yet been launched.

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