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Dear Reader,

We are pleased to launch *Italy Life Sciences 2021*, GBR's first Italian-dedicated report focused on the life sciences industries, including pharmaceuticals, biotech, medtech, digital therapeutics, nutraceuticals, diagnostics and packaging.

After a decade of successfully reporting on some of the world's largest pharma markets, including the US, India and China, GBR has turned its focus to Italy, a country heavily tested by the pandemic but that, we argue, has a unique opportunity to strengthen its role as an important European pharmaceutical hub. Italy does not have the span of US innovation or the scale of Asian manufacturing, but it is an essential API house to the American-European markets while boasting a characteristically strong research tradition. These qualities have never been as important as in a post-2020 world when the pharma industry and its lifesaving drugs have gained unprecedented public, political and investor attention, increasing the value placed on both drug security and drug innovation.

Italy has become the top European pharma manufacturer, on a par with Germany, as well as one of the biggest pharma exporters globally. Rather than driven by a handful of multi-billion Big Pharma businesses, Italy's industry has grown on the back of mostly mid-sized, often family-owned players. The production volumes speak for themselves, but Italy's innovation space is less known. GBR was pleased to learn about many Italian-born, breakthrough therapies that herald the transformation of modern medicine. But while Italy smartly leverages its manufacturing capabilities domestically and abroad, many of its original ideas remain trapped in the lab. At the same time, existing original and equivalent drugs are struggling with low-and-very-low market prices.

"Is Italy's healthcare system effective?" will likely yield different answers from patients, medical professionals, public authorities, and the life sciences industries. In this report, we look at the difficulties of trying to align these different stakeholders, and what this means for the industry. We also ask questions about how much and how well software can replace the pill and/or the doctor? What are the challenges around tapping into the rare diseases market? How are Italy's CMOs preparing to respond to ever more complex molecules? Under the "life sciences" title, we encompass a broad universe of products, from chemical drugs to cutting-edge stem cell therapies and AI-powered diagnostics, to hopefully offer a realistic guide to this very diverse industry.

Thanks to each of the 70 interviewees we spoke with during the course of our research, as well as to our partner associations for your time and support, and I wish everyone an informative and enjoyable read.

Alfonso Tejerina
Director and
General Manager
GBR

Lorena Stancu
Project Director
and Journalist
GBR

Mariolga Guyon
Project Director and
Communications Coordinator
GBR

ITALY LIFE SCIENCES 2021
Industry Explorations
Global Business Reports

A Global Business Reports Publication
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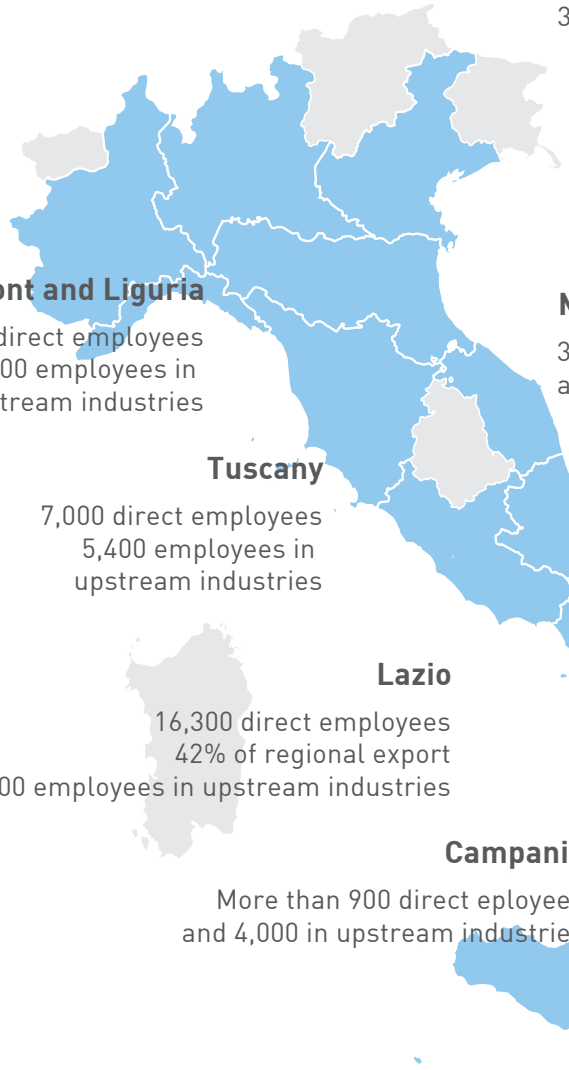
Project Director and Journalist: Lorena Stancu
Project Director and Communications Coordinator: Mariolga Guyon
Project Coordinator: Maria Filippova Barnachinskaya
Trainee Journalist: Susana Isotupa
Executive Editor: Mungo Smith
Operations Director: Miguel Pérez-Solero
Graphic Designer: Gonzalo Da Cunha
Layout and Ads: Özgür Ergüney
General Manager: Alfonso Tejerina

Lombardy

29,000 direct employees,
22,000 employees in upstream industries

Veneto

More than 3,000 employees,
9,000 in upstream industries;
30% of regional hi-tech export



Emilia Romagna

3,800 direct employees and 8,500 in upstream suppliers

Piedmont and Liguria

2,100 direct employees and 9,100 employees in upstream industries

Marche

3,400 employees in pharma companies and upstream suppliers

Tuscany

7,000 direct employees
5,400 employees in upstream industries

Abruzzo

1,500 direct employees (100 in R&D) and 1,600 in allied industry

Lazio

16,300 direct employees
42% of regional export
7,400 employees in upstream industries

Puglia

3,500 employees in pharma companies and related industries

Campania

More than 900 direct eployees and 4,000 in upstream industries

Sicily

About 1,000 direct employees and 3,000 in related industries

Source: elaboration of Istat, Efpia, Farmindustria data

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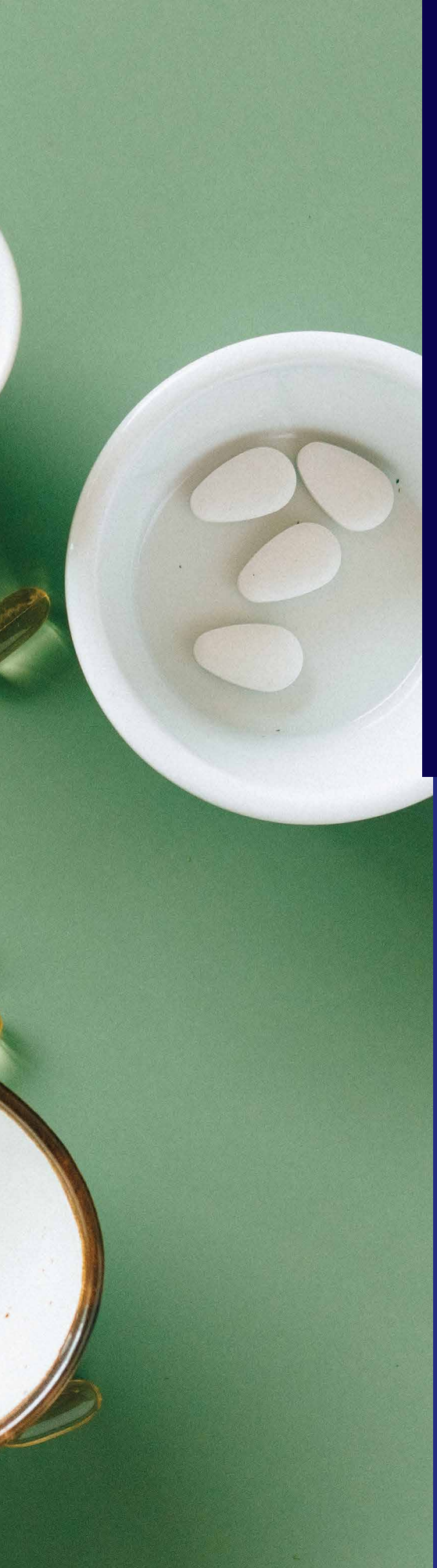


INTRODUCTION TO ITALY

"We need a new model, one no longer simply focused on containing costs, but oriented towards access to all available therapies. If we are to meet the shared health and growth goals, public health policies must be coordinated with industrial policy."

- Massimo Scaccabarozzi,
President,
Farmindustria

Image courtesy of Itel.

Introduction to Italian Life Sciences

ITALIAN HEALTHCARE'S URGENT RESPONSE TO THE PANDEMIC

Italy was the first European country to institute a national lockdown on account of the Covid pandemic. Italy's healthcare system showcased the heroism of its front-line workers, the massive mobilization of bed and personnel capacity, and the rapid response of its regulatory bodies to give a green light to Covid therapies. At the same time, many structural issues came to light.

Out of more than 4 million Corona virus cases, Italy registered a 2.8% mortality rate, higher than in other countries due to the high death rate amongst older people, who constitute a larger part of Italy's population. For people aged under 65, the death toll was under 1%, in line with other developed countries with an efficient health system at work.

Italy made exceptional efforts to manage the high number of hospital admissions, the entire health service being overhauled and its resources reallocated: Healthcare personnel were re-distributed across regions, retired doctors and nurses rejoined the hospitals, while recruitment tracks for medical professionals were sped up. The country almost doubled the number of ICU beds to respond to a peak of 34,000 Covid-patients hospitalized at the same time. More than 50,000 elective surgeries were canceled every week for a 12-week timeframe. Altogether, 75% of elective surgeries were suspended, according to a Nomisma report.

Today, over 70% of Italians are vaccinated, and hospitals are slowly seeing the "return to care," a phenomenon that is again problematic for health providers who need to catch up with the backlog of procedures and visits, as it is for pharmaceutical companies seeking to rebalance their stocks. Giovanni Sala, the general manager of Medac Pharma, observed the demand fluctuations for the hospital market, which is the company's primary focus: "The pandemic has significantly impacted the normal course of therapies, and consequently, we have seen reductions in sales volumes. Patients were either not able to or not willing to go to hospitals, delaying their examination and treatment.

The pandemic was an eye-opener for the system, a system that was left on the back burner for decades. Structural problems like the insufficient number of nurses and doctors or outdated digitalization were brought to the surface.

- Rodrigue G. Schübelin, Partner, PwC Italy Pharma & Life Sciences

In particular, we observed a slowdown of treatments in the urology segment and bladder cancer."
According to data from the German multinational, the number of surgeries performed since the pandemic declined by around 30%.
For Baxter (NYSE: BAX), the high number of Covid hospitalizations led instead to a growth in demand for products related to acute kidney injuries, with a quarter of ICU Covid patients developing this complication. Almost every pharmaceutical provider, in either the hospital or retail market, has experienced different combinations of low and high demand for some product classes in their portfolios. Even though demand is starting to stabilize as people return to their regular therapies, Sala reminds us that the pandemic has an "inertia effect," so the impact of the slowdown in some products may still be delayed.

Investing in healthcare

In the aftermath of the storm, healthcare undoubtedly became a key political and policy question. The pandemic exposed wide-ranging unpreparedness in dealing with the public health crisis in a continent where universal access to health is a central pillar of its society.
Italy's healthcare system reflects, to a great extent, the typical European model: free, universal, and arguably underfunded. In the EU's fourth-largest economy, health spending is lower than the bloc's average, according to WHO data: Italy spent 8.8% of its GDP on healthcare in 2017, against an EU average of 9.8%. The Servizio Sanitario Nazionale (SSN) or National Health Service (NHS) has seen various spending caps in the last two decades, mostly as austerity measures responding to the 2009 financial crisis. Despite consistent year-on-year budgetary increases, the overall healthcare spending trend has been conservative, aligned with a broader EU pattern.
That trend of moderate spending seems to be ending if we judge by recent developments: The European Commission approved EU's largest ever stimulus package known as NextGenerationEU (NGEU) – a mega-fund of 750 billion euros. Disbursed as the Recovery and Resilience Facility (RRF) mechanism, the program is aimed at building a post-Covid Europe by tackling investments in digital and green transitions, economic and social resilience (including health), and cohesion within the Single Market.
As part of the National Recovery and Resilience Plan (PNRR), Italy is one of the biggest recipients of the RRF among member states, cashing in a total of 68.9 billion euros in grants and 122.6 billion euros in loans. Out of this 200 plus billion euros bill, about 20 billion euros is allocated to healthcare reforms, said Andrea Fortuna, partner at PwC Italy Pharma & Life Sciences: "The healthcare fund is made of two main pillars. The first is directed at improving proximity networks, facilities and telemedicine for territorial healthcare assistance, while the second one, worth 11 billion euros, is dedicated to innovation, research, and digitalization within the NHS," he explained.

While NGEU is a short-term, high-impact instrument that encompasses healthcare in a more holistic way, the EU also launched a specific healthcare program that seeks to strengthen crisis preparedness and resilience. The EU4Health 2021-2027 vision is a fund to help Europe cope better with future shocks. The investment is directed to national stockpiling, building medical and healthcare reserves, as well as strengthening health data and communications amongst different national health systems.
Needless to say, Italy should benefit considerably from these funds which give public healthcare a chance to reform, modernize and democratize health provision across the width and length of Italy. The Italian life sciences industry - and especially its pharma and biopharma sector - is also presented with a great opportunity brought about by the rollout of these two programs, both directly and indirectly.

Time to shine

The Italian pharmaceuticals industry ranks in the top 10 pharma sectors in the world by value and is the EU's second-largest producer after Germany. According to Farmindustria's figures, Italy's total production value stood at 34 billion euros in 2019. However, Italian pharma players may not ring a bell as loudly as Germany's Bayer, Switzerland's Roche, France's Sanofi, or the American Pfizer or Merck. It-

aly's big names are of more modest market caps, including Menarini, Chiesi, Angelini and Recordati. But more importantly, Italy has a broad confluence of SMEs, both domestic players and foreign subsidiaries, which together make a dynamic ecosystem.

Starting with the PNRR, direct government funding in digitalization and innovation unlocks many opportunities for modern healthcare provision, including digital health apps or digital therapeutics. More significantly, the fund marks a change in attitude in favor of healthcare investment and, by extension, pharmaceutical investment, sending the message that life sciences is a backed-up, highly valuable, hugely impactful investment option. The unprecedented amount of funding in innovation will boost Italy's nascent biotech sector after vaccines stole all the attention in 2020-2021. Biotechnologies, advanced therapeutics including gene and cell therapies, but also support services like CROs and digital and sustainability actors will also be in the limelight of investors. Innovators across these segments are presented with the perfect momentum to raise money and channel the general attention towards specific projects after the world has attuned to the jargons of drug development, clinical studies and regulatory approvals.

Secondly, the EU4Health is premised on resilience-building, a fear-induced paradigm that has become incredibly powerful since the pandemic and that is shaking established principles on global order and the organization of trade. Reconsiderations over supplier origin and supply chain volatility put Italy in a favorable spot: Italy is the biggest API and CMO producer in Europe, the biggest part of its output being exported to Europe and the US. Italy could assert itself as a leading partner for Western producers and deepen its presence in the EU's high-value pharmaceutical chains. To Europe, Italy is a reliable and high-quality manufacturer that plays by the same rules, while producing at a lower cost compared to Western Europe. "Pharmaceuticals are one of Italy's key specialties and accounted for over 4 billion euros in positive trade balance in 2020," said Massimo Scaccabarozzi, the president of Farmindustria, Italy's main industry association.

By making itself even more indispensable to European pharma, Italy could accelerate the growth of its domestic pharma industry and support national economic growth. The country is on track to see GDP growth at 4.4% in 2022. "Rather than being seen as a cost burden, healthcare is now a strategic asset," started Andrea Fortuna, partner, PwC Italy Pharma & Life Sciences. "Every country in the world has learned that they must improve their preparedness and response to a health crisis like that of Covid-19. The Italian NHS continues to be recognized throughout the world as one of the most effective and efficient universalistic systems, but the Covid-19 emergency has shown the need to strengthen some key elements, also in consideration of demographic and epidemiological trends," he continued.

Fortuna's colleague, Rodrigue Schübelin, also partner at PwC Italy Pharma and Life Sciences, believes the way to correct what wasn't done well before the pandemic is by practicing long-term thinking in both corporate and political settings. Pharma companies are too much focused on short-term gains, while governments are too attached to yearly budget planning and tax collection. Social and climate governance should come first, he said. While optimistic about the funding put in place to revitalize Italy's economy, Schübelin warns about the increasing public debt, on its path to reach 160% of GDP by the end of 2021, and the signals this sends to investors and the industry: "There is a fear on the industry's side that the public money spent today will be collected back through taxes," he said.

The National Recovery and Resilience Plan (NRRP) fund is an intervention that aims to repair the economic and social damage caused by the pandemic, addressing the structural weaknesses of the Italian economy, and leading the country along a path of green and digital transition.

- Paolo Barbanti, CEO, Pharma and Biotech Advisors Srl

Political considerations

Italy's big recovery fund is much attributed to newly sworn-in-office Prime Minister Mario Draghi, a technocrat with eight years of experience leading the European Central Bank (ECB). The deployment and timely loan re-payment of these funds have wide consequences at both a national and European level because Italy is the eurozone's largest and possibly riskiest government bond market. Draghi has built a reputation at the ECB for steering the eurozone through difficult times after the financial crisis; his monetary policy reined in borrowing costs for eurozone governments and maintained low and even negative interest rates, sometimes controversially. Italy's tumultuous recent political past, spanning four Prime Ministers over the last 5 years, has only exacerbated economic, social and administrative issues, including a development gap between north and south, a broadly inefficient and bureaucratic public administration, compounded at times by cronyism, as well as high levels of public debt – the highest in the EU after Greece.

Shifting away from his predecessor's inclination towards China and Russia, Draghi's agenda is more centered on multilateralism and is looking West, towards transatlantic and Franco-German alliances. Italy's Europeanism and Atlanticism should serve the country's economic and trade relations, since Germany, France and the US are Italy's top export destinations. ■

After the crisis: thoughts from the industry

"The pandemic demonstrated that approval procedures can be simplified, and we ask for the same system that was applied during the crisis to stay on in the future."

- Enrique Häusermann, President, EGUALIA

"The approval process for new products in Italy is particularly slow, taking between 2-3 years to be complete, but the pandemic sped up this process. One year later, we see the same pre-pandemic sluggish process. The pandemic proved we can do things better, and this is the lesson that should pave the way for the future of pharma in Italy and elsewhere."

- Giovanni Mariani, CEO, Lisapharma

"The biggest opportunity for the industry is to help correct some historic flaws revealed by the pandemic and tailor to an ageing population through preventative care. Without health, there can be no wellbeing, personal or economic - This is the message the pandemic sent."

- Andrea Fortuna, Partner, PwC Italy Pharma & Life Sciences

"The pandemic has unlocked the necessary investments that will fuel the industry's growth, but also exposed gaps: We all became aware of the necessity to increase our manufacturing capabilities during the rush for sourcing the COVID-19 vaccines. This should encourage more fervent fund allocations in the years to come."

- Cosimo Lenti, Business Director, Diatheva

"Despite lower contagion levels in Italy, the fight against the pandemic continues, especially in the Global South. We must not confound the good situation we see in Italy with the end of the crisis, and instead start looking more broadly at both hemispheres in order to reach stability for the world at large."

- Maurizio Sartorato, CEO, Bidachem

"The unprecedented amount of funding and public attention presents us with favorable circumstances to deploy tech innovations. We must take action now and do it right because we may not meet with such an opportunity twice."

- Roberto Ascione, CEO, Healthware Group

Giorgio Palù

President
AIFA (ITALIAN MEDICINES AGENCY)

The main mandate is to guarantee access to medicines and their safe and appropriate use, but also to manage pharmaceutical expenditure in a context of economic-financial compatibility and competitiveness of the pharmaceutical industry.

Could you give us a brief introduction of AIFA's main mandate and most recent priorities?
The Italian Medicines Agency is the regulatory competent authority responsible for drugs in Italy. It iss a public body operating under the direction of the Ministry of Health and the supervision of the Ministry of Health and the Ministry of Economy. The main mandate is to guarantee access to medicines and their safe and appropriate use, but also to manage pharmaceutical expenditure in a context of economic-financial compatibility and competitiveness of the pharmaceutical industry. Furthermore, AIFA favors and rewards investments in Research and Development (R&D) in Italy, promoting and rewarding innovations. The strategic priorities are contributing to health promotion and protection through regulation of the marketing; use and supervision of medicinal products for human use; optimising the use of public resources allocated to reimbursement of medicines for human use to maximise the benefits of the community in terms of public health; promoting independent scientific information and fostering investments in research and development in the pharmaceutical sector.

Could you comment on Italy's bounce-back from the pandemic and the role of the agency in this task?
To date, more than 30 million people have been vaccinated (58,8% of the total population over 12 years old). The Agency and its Scientific Commission were and are constantly involved in the evaluation in a timely manner of new clinical trials protocol via accelerated procedures and also for the authorization of new possible therapies for the treatment of Covid-19. As a regulatory body, AIFA had a fundamental role in the approval of vaccines authorized at the central level by the European Medicines Agency (EMA). Furthermore, AIFA participates with its experts in the EMA working groups and manages vaccinovigilance through its national network (PhVig national network) and the European Eudravigilance network.

How is AIFA promoting clinical trials, innovation and R&D investments?
AIFA is committed to implementing the European directives and national legislation concerning clinical trials and ensures the functioning of the National Observatory on Clinical Trials for public and private research in Italy. The Agency publishes periodic reports and, in 2019, 672 clinical trials were authorized. The Agency promotes also no-profit clinical trials, aimed at showing the added value of new medicinal products compared to those available on the market. Since 2005, AIFA funded 288 studies and the most common areas are orphan drugs and rare diseases, comparative drug studies, new pharmacological strategies, active pharmacovigilance studies and pharmacoepidemiology studies.
Starting from 1 January 2017, two funds for participation in the reimbursement to the Regions were established; one for the purchase of innovative non-oncological medicines and one for the oncologicals. Each of these funds had an endowment of 500 million euros per year. A single fund worth 1 billion euros has recently been provided for these drugs.

How is Italy striking the balance between affordability and innovation when thinking about generics/biosimilars acceptance in the hospital and retail sector?
In Italy, generic medicinal products have a lower price than the reference medicinal products by at least 20%. Unfortunately, for a long time generics were considered to be different from the reference product and intensive information campaigns were launched in order raise awareness, especially among health professionals. These kind of medicinal products are of considerable benefit to both the NHS and the citizen. In fact, the savings achieved can be invested in the reimbursement of new innovative medicines.
The 2020 data on consumption of biosimilars confirmed the increase for those drugs whose biosimilar product has been commercially available for several years and this trend contributed to a reduction in expenditure. As regards the use of more recently marketed biosimilars, a positive trend was also recorded. (Anti TNF-alpha, bevacizumab, fast acting insulins, long acting insulins, rituximab and trastuzumab). The consumption, however, appears to be significantly different not only depending on the type of molecule considered and its indication but also according to the different regional situation.

Could you share a final message for the audience of GBR?
It is useful rethink new models and investments and use a good tax leverage to provide incentives for businesses and to encourage public-private partnerships. We invest primarily in digital health, innovation, training, start-ups, academic spin-offs and business incubators, research and intellectual property, data sharing networks (genomics, clinical trials) and, last but not least, internationalization. ■

Massimo Scaccabarozzi

President
FARMINDUSTRIA

> "The savings made in other health services thanks to medicines could be used to finance pharmaceutical spending. We need a new model, one no longer simply focused on containing costs, but oriented towards access to all available therapies."

Can you introduce Farmindustria's role to our international audience, and what are Farmindustria's most recent achievements?
Farmindustria is a member of Confindustria, Italy's main association of manufacturing and service companies. It is also a member of the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the International Federation (IFPMA). We have around 200 member companies, both national and foreign-owned. Our Association endeavors to create a stable regulatory environment and a pharmaceutical policy that recognizes the key role of our industry in the growth of the country's life sciences. Among our recent achievements, I would mention the close cooperation with our institutions, in areas such as the pandemic, where we have been able to assure continuity of all therapies for patients; spending ceilings, which will now be tied to actual expenditure trends; R&D tax credits; and the implementation of decentralized clinical trials, where we are conducting an in-depth study with the Italian Institute of Health.

How can Italy maintain its leadership as a European pharma hub?
Pharmaceuticals are one of Italy's specialties, as shown by the country's positive trade balance of over €4 billion in 2020, despite fierce international competition. Thanks to constant investments, our sector has increased its value add in relation to turnover and employees, as well as the average value of exports. We are internationally recognized for our high standards of safety and quality, coming from a long-standing industrial tradition. We want to keep creating innovative products (e.g., biotechnological medicines, vaccines, plasma-derived products, advanced therapies) as well as medicines with consolidated use that are key to the quality of patient care. Let us not forget contract development and manufacturing, where Italy is a European leader, and also the equipment manufacturing production chains.

How can market access for innovative drugs be facilitated in Italy's regulatory context?
It is crucial that the country invests more in pharma with respect to its growing demand for healthcare. The savings made in other health services thanks to medicines could be used to finance pharmaceutical spending. We need a new model, one no longer simply focused on containing costs, but oriented towards access to all available therapies.

How do you think the pandemic shifted attitudes towards healthcare and the life sciences industry?
We have learned that health is wealth, freedom, work, and equality. Without health and investments in the life sciences there will be neither a future, nor social development. Public and private systems need to create a network where skills, planning, rules, and decision-making processes coalesce to attract investments. Public health policies must be coordinated with industrial policy.

How does Farmindustria encourage youth training and development through initiatives like Alternanza Scuola Lavoro or Higher Technical Institutes?
We realized that it is urgent to prepare our youth for their future careers by equipping them with the right skills. That helps us tackle the problem of school drop-out and the complex phenomenon of NEETs [not in employment, education or training].
Alternanza Scuola Lavoro is a three-year project involving high school students, realized through a strong partnership with the Ministry of Education, territorial associations, and unions. Students are guided by our member companies and they are provided guidance on the continuation of their studies, as well as workforce entry. The program has reached hundreds of students so far and we are now extending its reach to cover all of Italy.
As for HTL (ITS), issues like skills mismatch led us to develop a program where we could facilitate the development of new skills required to meet the needs of digital transformation, and thus fill hard-to-find professional roles that our industry requires to continue its growth. These are 2000-hour courses, of which 900 is on the job, where teachers are 90% company experts.

How is the Italian pharma sector positioned to address the 2030 Sustainability goals?
Our companies offer one of the most advanced and comprehensive corporate welfare programs for an optimum work-life balance (e. g. assistance to non-self-sufficient family members; educational, social and health assistance services; collective transport; company canteens), plus programs that help employees acquire multi-disciplinary skills. Women are especially valued, representing 43% of pharmaceutical employees, well above the national average (29%). Moreover, women account for 42% of our executive and middle management roles and 52% of R&D jobs. ■

Connected Healthcare

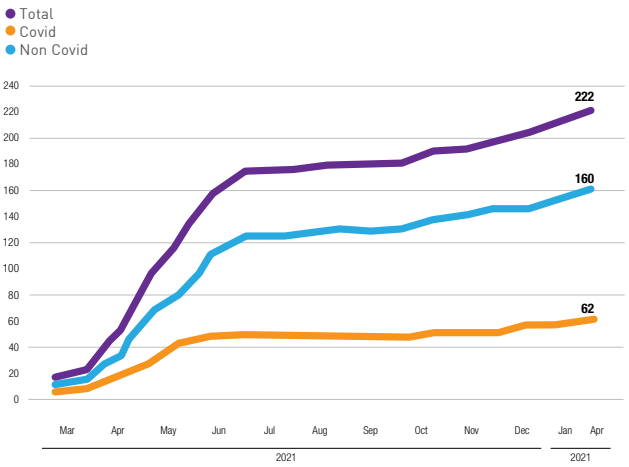
THE PUSH FOR DIGITAL HEALTH

By WHO definition, digital health is the "delivery of health care services where distance is a critical factor." Because distance became a very critical aspect during the pandemic, everything under the umbrella of digital health, from the basic e-prescriptions to advanced digital therapeutics (DTx), made important leaps in 2020. Pharma companies and healthcare providers also made steps towards these technologies. In Italy, 47% of specialist doctors and 39% of GPs made teleconsultations during the pandemic last year, according to a report by Observatori.net. For instance, ASST Grande Ospedale Metropolitano Niguarda launched a televisit project to provide follow-up examinations to bedridden patients. Some Italian hospitals also used apps to monitor patients or bought inpatient remote monitoring kits to reduce direct contact. Globally, IQVIA reports that 90,000 new health apps were launched in 2020.

The pandemic became instrumental in digital adoption and the shift to telemedicine, fostering investments in infrastructures like mobile apps for contract tracing and social distancing. The crisis became an opportune time to test the use of existing technologies to a wider scale and to push new technologies into being; but the practice of telemedicine, as well as the use of digital apps, have broader applicability beyond the pandemic, especially when it comes to the management and treatment of chronic disease patients. Pagine Mediche is Italy's largest medicine platform and the first to create a Covid-19 chatbot globally. A recently published observational study indicated that the platform could predict spikes in the virus two weeks ahead of other KPI indicators. The same data collection apparatus could have great applicability in other disease management. IQVIA confirms that almost 50% of health apps are now focused on helping customers manage current health conditions like diabetes, mental health, or cardiovascular diseases, rather than focusing on wellness alone.

Traditional medicine saw the interactions between doctors-patients, pharmacies-patients, doctors-pharma suppliers, and patients-other patients, isolated and linear. But digitalization gives rise to a third dimension in which doctors, patients, pharmacies and pharma suppliers can interact and engage via multiple channels, and which the pharma companies, as the sole supplier to all three parties, can exploit and incorporate in their working models.

Telemedicine Initiatives Launched in 2020-2021



Source: Osservatorio ALTEMS, 2021

In 2021, Italian company Alfasigma opened a support engine solely dedicated to physicians; "Doctors as You" works as an aggregating portal for online scientific research, also offering medical training development. On the customer-facing side, innovative pharma company NTC Pharma inaugurated NTC4You, which is already used by 80% of its customers, proving a real need in the market for such service. It is becoming more common for pharmaceutical companies, big and small, to develop digital channels and links vis-à-vis both the medical community and the patient community, oftentimes defining such communities digitally. Besides running a digital portal to share information with practitioners, Sicilian innovator SIFI Group pioneered a sound system for visually impaired customers who can listen to the information on the leaflet by scanning the QR code on the packaging.

These types of close-patient engagement, facilitated by digital, are characteristic of a new healthcare model which puts the patient at the centre; akin to a consumer, the patient is presented with solutions, rather than mere products. Roberto Ascione, the CEO of Healthware Group, elaborated: "The life sciences company of the future will be focused on the patient's journey, creating meaningful patient and consumer experiences, as well as implementing early diagnostics and data. In this scenario, tech companies, health insurers, and drug makers will be competing for the patient's attention. I call this approach a shift from cure to care as part of a seek-and-care healthcare model, much more focused on prevention and wellbeing."

From cure to care

Harmonium Pharma is an Italian company founded in 2013 dedicated to diabetes, a chronic disease affecting over 420 million people globally. Unlike the usual diabetes-focused company offering insulins or sugar monitoring devices, Harmonium instead focuses on the day-to-day management of the disease with everything that entails: "Besides the pharmacological therapy itself, chronic disease management also involves two other aspects: education and prevention. These are the areas where we position ourselves, seeking to create tighter links with the patient," said founder and president Ugo Consentino.

Chronic disease management has been traditionally left to the doctors and patients/caregivers, but pharmaceutical companies are playing a growing role in offering care, a role that is going beyond the offer of chemical, biological, or natural products. The Italian subsidiary of French company Ipsen launched the first website tailored to patients suffering from spasticity, a lingering side-effect occurring after a stroke. "Beyond spasticity" gives patients a go-to place to understand and manage their symptoms. Similarly, UCB (EBR: UCB), one of the world's biggest pharma companies with strong expertise in immunology and neurology, uses digitalization to connect with epilepsy patients. UCB invested in Nile AI, a digital health company for the care management of epilepsy.

Besides the service-like approach of such platforms, which offer awareness, practical advice, training, and perhaps even solidarity and a sense of belonging to a wider digital community, pharma companies are also deploying DTx used in the management of chronic diseases.

Healthware Group, one of the world's largest independent healthcare consultancies, has developed together with Finnish company Orion Corporation a VR-based therapeutic used in the management of severe chronic pain. Roberto Ascione, Healthware's CEO, expects a serious marketplace transformation whereby pharma companies will not only be selling drugs, but also drugs plus software, and software-only therapies: "Sooner rather than later, approved prescription DTx will be either software alone or software plus pill, and my view is that the software will play the lion's share of the therapy," he said.

The ultimate revolution for the industry will be the shift from a product-centric business model to one of 'solutions' that blend products and services tailored to precise needs.

- Stefano Collatina, Country Lead, Baxter Italy

We seek to put patients at the same decision table with other stakeholders for decisions regarding their therapies. We consider that patients are experts of their disease, but not necessarily experts in hospital budgets or clinical terms, so we want to help them understand the medical jargon and input their views.

- Federico Chinni, CEO Italy, UCB Pharma

Digital platforms, apps and DTx do not replace specialists, but they do create a third space, a digital one, as well as defining (and re-defining) physical spaces, including the home, the hospital, and the pharmacy.

When Draghi covered in his speech the allocation of one billion euros to telemedicine as part of Italy's recovery fund, he argued that telemedicine could make "the patient's home the main place of care." The pandemic clearly deterred chronic patients from visiting hospitals, and the reputation of hospitals as unsanitary may well persist past Covid. Stefano Collatina, Italy's country lead of Baxter International, believes the perception of hospitals as hotbeds for viruses and bacteria will lead to the emergence of "out-of-hospital" care centers for chronic treatment, whereas the hospital shall remain secluded for acute and emergency treatment.

Meanwhile, the pharmaceutical space is also transforming. According to Ugo Consentino from Harmonium Pharma, two types of pharmacies coexist today: the traditional one focused on straightforward drug provision and aggregating a large and diverse drug supply; and a second type that works as the first point of contact to the patient and whose personnel is trained in providing advice, diagnosis and consultancy. Harmonium Pharma sells its portfolio package under the "Diabetic Corner" brand to this second category of pharmacies: "Our partner pharmacies are not just a place where the patient can pick up prescriptions, but also a space to receive advice from trained staff, or even attend screening events or activities to raise awareness about the disease," he explained.

Regulatory validations

For all its merits, digital health cannot gain traction without the support of regulators and digital infrastructure. A recent study published in the Journal of Medical Internet Research found that the lack of clarity around telemedicine reimbursement inhibited a wider-scale adoption of telemedicine in Italy during the pandemic. Provisions for telemedicine had been introduced in the country since 2012 through an agreement between the government and the Regions known as "Telemedicine-National Guidelines" and last year, the government released other interim indications paying particular attention to televisits. In September 2020, The Health Commission of the Conference of Regions adopted a guideline identifying the conditions for remote medical assistance, which should make the reimbursement codes more explicit and easier to follow.

However, while telemedicine is a more mature sector, DTx and the incorporation of software to treat, prevent, or manage a disease is a much less known terrain to which regulators around the world must learn to respond. There are 150 digital therapeutics currently available, and another 100 in development. Though not directly linked to the treatment of Covid, DTx's ability to deliver medical interventions directly through patients and providing data-feedback is gaining significant importance in a patient-empowered, data-driven, and increasingly remote healthcare model.

Last year, Germany was the first to introduce a reimbursement model for DTx, after having already passed in 2019 a provision allowing doctors to prescribe digital health apps to patients. These are reimbursable by the state. A DTx law is not existent yet in Italy, but Ascione believes this is underway. The CEO of Healthware Group and the founding adviser of Digital Therapeutics Alliance collaborated on a white paper put together by Tendenze Nuove to define the framework for DTx in Italy. Ascione thinks legal implementation should and must follow: "Many actions that had been waiting for the past 20 years were finally set into motion by Covid-19. (…) Global healthcare is dysfunctional and unequal, and digital is the sole way that healthcare can be effective and sustainable, especially as we could potentially confront bigger crises if we judge by global demographic changes combined with climate change."

Image courtesy of ISE.

Digital health market

2020	2021	2022	2023	2024	2025	2026	2027
>$141.8 BN			CAGR (2021-27): 17.4%				>$426.8 BN

Market Value (2020)

$50.5 BN	>$56.4 BN
Service segment	Mobile Health segment

North America market CAGR (2021-27): 16.2%	Europe market share (2020): 34.6%

Source: Global Market Insights

Digital health could relieve the overburdened Italian healthcare system by triaging patients to televisits or digitally assisted therapies, as well as by replacing, where possible, the work of the practitioner. Italy has the largest share of medical doctors aged over 55 among all OECD countries, according to OECD Health at a Glance Indicators (2019), and a lower number of nurses compared to most European countries. Digitalization also helps with reducing the time for in-person medical visits, as Federico Chinni, the country lead of UCB Italy explained: "The first part of any doctor visit is filled with administrative tasks, so by registering drug history or symptomatology through the app, the consultation time can be more effectively spent."

Ultimately, digital health is important for the patient. The IQVIA report "Digital Health Trends 2021" found that digital tools have an increasingly positive impact on health outcomes. Finding effective means to promote adoption is therefore crucially important. In some cases, limited adoption does not permit the takeoff of digital apps: for instance, the Italian Immuni app introduced to act as a surveillance system in June 2020 didn't lead to the desired effect because not enough Italians downloaded it. About 12 million have downloaded the app as of today. ■

Rodrigue G. Schübelin & Andrea Fortuna

Partners,
PWC ITALY PHARMA & LIFE SCIENCES

> **The pharma industry once again stands out as an anti-cyclical safe harbor investment and one of the few industries that thrived in what has turned out as the biggest recession since the Great Depression.**

Can you tell us about PwC's life sciences branch in Italy and your core activities?
RGS: The Pharma and Life Sciences division at PwC Italy is one of the key industries where we embed our service offer across a wide range of competences. Given that the health industry generates some €110 billion growth revenues and hence contributes to about 10% of Italy's total GDP, the pharma sector is an important economic driver; PwC dedicated professionals in all lines of work, from assurance services, to consulting, deals tax and legal to serve this strategic industry.

The healthcare system was put under a lot of pressure with the pandemic, in Italy as elsewhere. How is the Italian public sector mobilizing to create greater resilience in the future?
AF: The healthcare sector has gained greater centrality in the political agenda; rather than being seen as a cost burden, it is seen now as a strategic asset and an essential pillar to ensuring better quality of life and socio-economic development. The Italian NHS continues to be recognized throughout the world as one of the most effective and efficient universalistic systems, but the Covid-19 emergency has shown the need to strengthen some key elements, also in consideration of demographic and epidemiological trends. The Italian Recovery and Resilience Plan (PNRR), financed with over 235 billion euros, represents a unique opportunity. It is divided into six missions, one of which is specifically dedicated to Healthcare (20 billion euros). The funds are aimed at two main pillars: the first is to improve "Proximity networks, facilities and telemedicine for territorial healthcare assistance", that includes home care, long-term care and primary care. 9 billion euros are dedicated to this first mega-goal. The second pillar worth 11 billion euros is dedicated to innovation, research, and digitalization in the NHS. This will entail the update of technological equipment and infrastructure, the improvement of the health information systems and digital tools. One billion euros will go into training, biomedical research and tech transfers.

What drives M&A activity in Italy and what are the most sought-after pharma assets?
RGS: The pharma industry once again stands out as an anti-cyclical safe harbor investment and one of the few industries that thrived in what has turned out as the biggest recession since the Great Depression. Innovative biotech, cell and gene therapy, oncology and rare diseases are attracting the most interest and are seeing extremely high valuations. Liquidity is certainly in the market, so the challenge is to identify a distinctive target; when the chase starts, there is fierce competition in closing the deal. In 2020, Menarini, Italy's largest pharma company completed the biggest acquisition in its history in the midst of the 2020 Covid-19 lockdown, which shows the capacity of the industry to address boldly and strategically times of crisis by seizing the opportunities it brings along.

Where do you see as the biggest opportunities in the Italian life science industry?
RGS: The biggest opportunity for the industry is to help correct some historic flaws revealed by the pandemic and tailor to an ageing population through preventative care. After an 18-months delay during which people did not go to see their doctors for diagnostics or treatment we see nowadays the "return-to-care" as one of the key challenges and opportunities for the entire Health industry.

What are your main priorities for the next 2-3 years?
AF: In supporting as Knowledge partner of the Health & Life Sciences task force of B20 that will be held in Italy in 2021, one of the main discussions taking place is how to maintain the momentum (e.g. accelerated routes to investigate and adopt Research and Technology) and implement the lessons learned during this difficult period to contribute to the development of the sector in the future. Our mission at PwC is to "build trust in society and solve important problems" and, with that said, our ambition is to keep being an important player in a sector that is increasingly more preeminent in Italy's economical, political and social agenda. ■

Roberto Ascione

CEO,
HEALTHWARE GROUP

> **Digital is the sole way that healthcare can be effective and sustainable, especially as we could potentially confront bigger crises if we judge by global demographic changes combined with climate change.**

Healthware was founded 25 years ago and grew into one of the world's largest digital health players. Could you tell us a few words about the company and its mission?

For a long time, Healthware has worked at the intersection of the digital transformation of the life sciences. We have always looked at one fundamental issue: how to improve health outcomes through the use of technology, directly or indirectly.

We were one of the first organizations in Europe to build a digital awareness website when we started in the mid-nineties, together with the rise of the internet. Though we're based out of Italy, our main markets are shared between Italy, the UK, and Finland. Italy accounting for about 20% of our total revenues.

Now we are a global leader in healthcare digital innovation, combining innovative R&D capabilities focusing on digital medicines and digital therapeutics, with commercial and medical operations for our own products and services as well as for established and emerging life-sciences and DTx companies and other healthcare stakeholders.

Proprietary software platforms, specialized media and educational assets as well as a corporate venturing arm, ensure accelerated product development, close integration within the innovation ecosystem, continuous pipeline development and market access.

Healthware has evolved to offer digital therapeutics (DTX) products co-developed with industry partners. Could you elaborate on this expertise and share some recent project examples?

Besides our service go-to-market offer to pharma and medical devices companies, we are also producing end-to-end DTX, always together with our partners. Applying our accumulated patient-centric innovation designs and our experience of running predictive analysis and behavioral modification processes, Healthware Therapeutics acts as a digital pharma company.

We recently worked with Paginemediche, Italy's largest medicine platform that created the first Covid-19 chatbot globally. After one year of data collection since opening the open platform in Italy, the Journal of Medical Internet Research (JMIR) has approved for publication an observational study showing that the platform can predict any spike in the virus two weeks before any other available KPI indicator. This technology could have immense applicability in chronic disease monitoring. The observational study was done with the Rome-based Bambino Gesù hospital.

Another example is a VR-based treatment for severe chronic pain, developed for the Finnish company Orion. This DTX largely outperforms the gold-standard chemical treatment and is a huge breakthrough for pain management.

How do you observe the uptake of DTX by the industry?

In the past four or five years, the industry has come to realize there is an imminent and radical marketplace transformation whereby they will be marketing not just drug-based interventions, but also drug + software interventions, as well as software-only interventions. Sooner rather than later, approved prescription DTX will be either software alone or software plus pill, and my view is that the software will play the lion's share of the therapy.

More companies are starting to invest in DTX start-ups, running in-house innovation programs, or looking at partnerships.

How do you see the life sciences company of the future and what is Healthware's role in this sense?

The life sciences company of the future will be focused on the patient's journey, creating meaningful patient and consumer experiences, as well as implementing early diagnostics and data. In this scenario, tech companies, health insurers and drug makers will be competing for the patient's attention.

Healthware evolved dramatically over the past five to six years through acquisitions, so today we brought in more components that ultimately lead to that same mission: making sure that the future of healthcare looks very different from the past. My vision is not delivering drugs, but empowering people to stay clear of diseases by caring about each person, individually and on their own terms. I call this approach a shift from cure to care as part of a seek-and-care healthcare model, much more focused on prevention and wellbeing.

Could you share a final message with our audience?

Digital is the sole way that healthcare can be effective and sustainable, especially as we could potentially confront bigger crises if we judge by global demographic changes combined with climate change.

The unprecedented amount of funding and public attention presents us with favorable circumstances to deploy tech innovations. We must take action now and do it right because we may not meet with such an opportunity twice. ■

Teresa Minero

Founder and CEO,
LIFEBEE

> **Many opportunities enabled by new technologies are there to be harvested. A big challenge for management is often to decide what to prioritize and how to create the best sequence of projects, based on financial and staff resources and also its own digital maturity.**

Can you provide an overview of LifeBee's service offering?
Together with our customers, we effectively redesign information flows, procedures and digital solutions, but also materials/personnel flows and organization, extensively combining operational excellence, proactive compliance and digital transformation approaches. The focus is on GxP regulated areas such as manufacturing, quality assurance, laboratories, logistics, serialization, regulatory affairs and pharmacovigilance of biopharma, medical devices and nutraceuticals companies. In consulting, LifeBee operates by means of process review interventions with the goal of process optimization, digital innovation, GxP compliance and data integrity and pharma 4.0 strategic plans. In digitalization, LifeBee provides projects feasibility studies, vendor selection, project management and the realization and support of digital solutions for both R&D and operations.

LifeBee was recently appointed "Top Laboratory Automation Solution Providers in Europe 2021". Could you explain through a specific case study how LifeBee can support life science companies on their path towards digitalization?
We were delighted to receive this recognition as it represented the acknowledgement of the many successful projects delivered to Life Science Labs.

One recent 10-week case study we are proud to share is the Conceptual Design for a pharma multinational company - aimed to optimize the whole Lab including processes, personnel and material flows for a new facility dedicated to a pharma Quality Control Lab (2000 square meters, 40 resources, 220 instruments). A key aspect is the focus on personnel and the instruments capacity to define the best lab layout, personnel organization, instrument pool and investment budget. A dedicated implementation plan has been prepared to be submitted to the Regulatory Agency for approval, considering the discontinuation of the old Lab while maintaining the entire business continuity - no analysis delays or related batch releases will be accepted.

The pandemic has greatly accelerated the digital transformation of the pharmaceutical industry. Can you highlight some emerging trends you are observing in Italy in terms of IOT, robotics and big data?
The Covid-19 tsunami has further showcased how digitalization plays a central role in making remote work possible in total compliance also within Life Sciences, as long as you have adequate digitalized infrastructure and application portfolio, all designed to really enable effective operability and robust compliance, with strong integration and with procedures and trained personnel in place. In short: a true digital transformation.

4.0 in Pharma is an objective "leap" also in Italy. We increasingly see successful projects using IOT (Industrial Internet Of Things), regulated cloud applications, on-demand and big data analytics and collaborative robotics: technological innovation in continuous improvement in a well-structured and ingenious way. This results in a long-lasting perspective regarding innovation and is part of the progression in the last few years in Italy's role as a leading medicine producer in the EU and as a major exporter.

How has the demand for your services evolved in recent years?
In the last five years we have constantly grown by 20% on average, much higher than the market. I would interpret this as the result of our unique selling point: we are not only a digital company, nor validation or compliance firm, nor exclusively Lean consultants. We are three in one and this is the key differentiation that our customers choose.
In addition, there is evermore the need to guide our customers in their journey towards digital transformation. Many opportunities enabled by new technologies are there to be harvested. A big challenge for management is often to decide what to prioritize and how to create the best sequence of projects, based on financial and staff resources and also its own digital maturity. The design of sustainable and robust 4.0 and digital roadmaps is becoming one of our bestsellers as consulting services.

What are LifeBee's priorities for the next 2-3 years and do you have a final message for our international audience?
Our priority is to increasingly extend LifeBee services at an international level, starting from a customer base of 70 companies that on average already export 85% of their production. Following the needs of our customers we deliver 15-20% of our services outside Italy. I have been recently nominated as one of the "Top 25 Healthcare Tech CEOs" in Europe. This stands as a remarkable recognition for our team's work and surely looks promising for our future plans. ■

PRODUCTION

"The Italian market is well-served and patients benefit from great service. To sustain this level of service, all stakeholders must recognize that having first-in-class drugs on the market requires a system that will continue to attract investments in research. The role of the generic products is fundamental in contributing to freeing the necessary resources."

- Giovanni Sala,
General Manager,
Medac Pharma

Image courtesy of SIFI.

The domestic sector

HOMEGROWN PHARMA READY TO EXPAND

"The Made in Italy label speaks not just of Ferrari or Gucci," started Luca Crippa, the CEO of IBSA Farmaceutici. Crippa makes reference to the country's pharmaceutical industry, which is battling with Germany for the title of EU's largest producer. When it comes to exports though, Italian pharma is a safe winner as the fifth largest drug exporter in the world.

Out of the 200 pharma players active in Italy, almost 60% are foreign-owned. No one company can be said to be dominating the market, but Big Pharma like AbbVie, AstraZeneca, or Bayer all enjoy leading market shares, according to a report by Mordor Intelligence. Next to these companies, Italy has grown its own "Grande Pharma." Menarini is the largest in the country and 37th biggest pharma company globally by turnover. Angelini, Chiesi, Recordati, Bracco, Alfasigma, Zambon Group and Leadiant Biosciences follow, with turnovers ranging between 500 million and 3.6 billion euros.

A typical feature of the Italian market is the enduring family legacy. Italy is one of the countries with the most family-owned businesses, reports the Credit Suisse Family 1000, and pharmaceutical companies make no exception. Also, many of the leading pharma companies today are the result of a century's development. Menarini was founded in 1886, Zambon in 1906, Angelini in 1919, Recordati in 1926, Bracco in 1927, and Chiesi in 1935. Some of these have belonged to the same family for generations.

With an offer of both small and large molecules, as well as medical devices and med-tech, these MNC-status players typically cover the chronic therapeutic spectrum, from cardiology, respiratory, urology, gynaecology, pain, neurology, but also oncology and rare diseases, the last two sparking considerable interest recently. For example, Menarini is studying precision medicine for cancer treatment, while Chiesi is opening a new rare disease division. By ramping up R&D efforts and eyeing the right partnerships and acquisitions, Italy's homegrown pharma are looking to climb up the ranks and reach global acclaim.

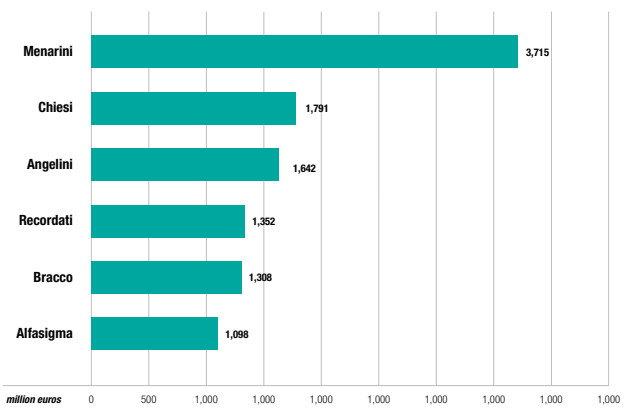
Top five Italian player Alfasigma wants to enter the list of the biggest 100 pharma companies globally; to do so, it will have to jump 18 positions from where it currently sits. The multinational with a 2020 turnover in excess of 1 billion euros and a presence in 70 countries is fiercely investing in innovation and strategic acquisitions: "We are inaugurating a new R&D facility in September 2021, which will help us reaffirm our focus on gastroenterology, vascular diseases and neuroscience as well as expanding our biotech capacity, looking closer at rare diseases," said Giuseppe Allocca, technical operations executive director.

The company also acquired the rights to commercialize bentracimab, a new monoclonal antibody developed by the American company PhaseBio Pharmaceuticals. The molecule will be marketed by Alfasigma in 49 countries. This year, Alfasigma acquired the rights for Lumeblue from Cosmo Pharmaceuticals, an Irish-based company with Italian roots. Lumeblue was recently approved by EMA to be used for the detection of lesions during colonoscopies.

M&A activity in the country was complicated – to say the least – by the pandemic, but this has not stopped historic transactions. Menarini made the biggest acquisition in the company's history, buying Stemline Therapeutics, a clinical-stage biotech player focused on stem cell oncological therapies, for US$677 million. For an even more impressive sum of US$960, Angelini also announced the acquisition of Swiss company Arvelle Therapeutics. One Angelini executive commented that this is one of the company's most important investments since it was founded in 1919. The buyout will give Angelini the licence to market cenobamate in the EU, the UK and Switzerland, once the drug is approved by EMA. Cenobamate is an oral drug used for epilepsy, already approved by the FDA as an anti-seizure medication. Meanwhile, Chiesi bought US company ApoPharma. Chiesi was already distributing ApoPharma's Ferriprox (deferiprone), a drug used in the treatment of iron overload in thalassaemia major (a genetic disease also known as Cooley anaemia). By taking full hold of the company, Chiesi expands its presence in rare diseases and enters the Canadian market for the first time.

Evident from these acquisitions is that Italy's biggest pharma companies look for advanced innovations to add to their portfolios, especially in the sphere of biotech. The

Top Italian Pharma Companies



Source: Statista 2021

pandemic might have been the best opportunity to make these investments: Besides the fact that the pharma industry is one of the most resilient during crises, making pharma stocks a safe harbor investment, pharma, and especially biopharma, became uniquely central during the pandemic. The search for a vaccine and the media's close follow-up on each research development created anticipation and awareness about the significance of discovering life-saving drugs. Public perceptions on pharma improved, while pharma investment became a much more appealing option.

In investment terms, these positive appreciations are reflected in stock performance. The Dow Jones US Pharma Index (DJUSPR) saw a 19.29% year growth. Listed on the Italian Stock Exchange (Borsa Italiana), many Italian companies saw their share prices grow over the past year. Urology and rare diseases player Recordati (BIT: REC) had a one-year performance of +20.47%, for example. In the medical equipment and technology space, laser solutions supplier El.En saw a +117.39% one-year appreciation. Nutraceuticals and naturally derived products were also well-valued by investors: PharmaNutra (BIT: PHN) graduated to the STAR-MTA of the Borsa Italiana, only three years after joining the AIM. STAR is the segment of the Italian Stock Exchange for companies with a market capitalization of between 40 million and one billion. "Liquidity is certainly in the market," said Rodrigue Schübelin, partner of PwC Italy Pharma and Life Sciences. The challenge is, he continued, to find a good target: "Innovative biotech, cell and gene therapy, oncology, and rare diseases are attracting the most interest and are seeing extremely high valuations when considering EBITDA multiples."

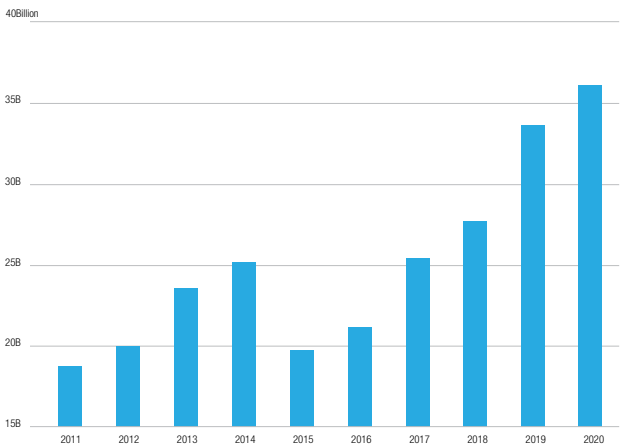
As big players fight to stay on top of a competitive, evermore-complex industry by looking at collaborations with R&D centers, distribution partnerships and acquisitions of high-tech assets, Italy's native biotech sector as well as its supportive CMO sector should also benefit. Aside from getting hold of next-generation innovations, the other driver of M&A is international growth.

Italian pharma wears export labels

The Italian pharmaceutical market is poised for modest growth of CAGR 3.5% between 2019 to 2022, according to Statista, much slower compared to a high global growth of 11.3%, driven especially by North America and Asia, based on GrandViewResearch. Italy's slow growth is suggestive of a mature and competitive market and is closer to Europe's projected 4.5% CAGR to 2022, as reported by Evaluate Group. While overall growth in the industry is more stifled compared to the rest of the world, exports have been the real growth story:

Italian pharma exports have been growing exponentially for decades: between 2010 and 2017, pharma exports grew at 26% every year, while the European average stayed constant at 1%. Farmindustria estimates that over 80% of Italy's total manufacturing value comes from exports. This brings the total revenue generated by foreign sales at 70%, informs Eurostat.

Italy Pharma Exports 2010-2020



Source: TRADINGECONOMICS.COM

Italy is Europe's fifth-largest pharma exporter, after Germany, Switzerland, Belgium, and France, together with whom it makes Europe the strongest pharma exporter in the world, followed by the US. Exports are Italy's strongest advantage, a testimony of the quality and appreciation Italian-made products receive on the globe, but also a very strategic advantage for the country's trade balance. On the ground, the focus on exports is easy to note. Almost every company with a good grip of the Italian market will look over borders to grow its business. Europe, the US, Japan, Korea, but also Russia are some of the usual suspect export destinations. In 2019, the US was the leading export destination, followed by Belgium. "The life sciences industry is moving at two speeds: the US and the rest of the world," said Gilda D'Incerti, CEO and founder of PQE Group, a Florence-based consultancy with over 20 offices globally. "The pandemic truly showcased the strength of the US industrial machine, the US industry responding much faster compared to Europe."

The huge market and attractive prices make the US the preferred export destination for EU pharmaceuticals, but market preferences vary depending on many factors, and some players will even stay away from crowded markets. Mar-Farma, an Italian player selling food supplements and medical devices primarily in women's health, has a very clear international focus, 80% of its sales coming from foreign markets, specifically the Middle East and Africa. "We are present in many countries where other Italian players do not venture to, such as Yemen, or in countries where companies do not sell their products due to political reasons, such as Iran. Mar-Farma's priority is to take care of the wellbeing of people, independently of the political context," said Roberto Ricatti, the CEO.

For Harmonium Pharma, another Italian OTC supplier, choosing the target markets comes with different considerations: because its products are out-of-pocket premium

solutions, Harmonium Pharma places its Diabetic Corner offer in countries with the right socio-economic demographics. "From a consumer perspective, our target markets are countries that meet the right balance between a large diabetes population and a high cost-of-living index," said Ugo Cosentino, president and founder.
Moreover, Ugo looks at diabetes incidence, which is highest in the Middle East where up to 30% of the population suffers from the condition. China, the US, Mexico and Brazil also meet those large-scale considerations.
Similarly, Italian company Nerviano Medical Sciences (NMS) Group, a leader in kinase inhibitors used in cancer treatments, has even more sophisticated, genetic models to understand and tailor to market needs, for instance by studying the incidence and typology of cancers in some regions of the world such as China: "Taking note of interethnic genetic differences, we started to focus on cancers that are more common in Asia, such as lung, liver, and stomach cancers," said CEO Nanding Zhao.
Other times, finding a spot in the global market is mostly about creating a niche. Founded in 1882, Candioli is one of the oldest Italian pharma companies. 20 years ago, it reinvented itself by transitioning from human health to animal health, where it found an underexplored and rich market. Luca Candioli, the fourth-generation owner, believes the veterinary space has incomparable growth potential: "There is no other sector with the same level of demand. Buying a puppy of the desired breed today can come with a one to two years waiting list in some countries," he said.
As a market leader in Italy, Candioli is already achieving maximum growth domestically, so to double its size in the next five years as it plans to do, the company checks international markets. A few years back Candioli bought UK company Vetark, setting up its first international affiliate and combining the two portfolios. The company is looking to make another acquisition in Europe and repeat the Vetark experience.

The next step in our internationalization process is to strengthen our commercial agreement with countries that value specialty care. Meanwhile, through our group company, Quotalia Science, headquartered in Serbia, we will facilitate penetration in emerging markets.

- Paolo Gobbi, Founder and CEO, Haemopharm Healthcare

Expansion strategies

Well-established players with a widespread international presence and a good understanding of the different markets can already look at establishing a direct presence in key markets. San Marino-based company Erbozeta distributes its food supplements and medical devices portfolio in about 70 countries, and it recently opened a third international office, this time in Portugal. While its Austrian office helps with market access in the EU, and its Hong Kong office is a hub for the Asian markets, Portuguese Erbozeta Iberica acts as a bridge across the Atlantic, dealing with patent registration and protection for its Latin American markets. This strategic mapping allows the firm to regionalize its reach and have not one, but multiple international strategies.
Nevertheless, even for those with a wide international footprint and numerous subsidiaries, distributors are the key to successful and extended market penetration. Even though IBSA's network covers up to 80 countries, not all of its 200 generic products enjoy this widespread footprint: "IBSA has a much broader basket with a local footprint and we'd like to launch these products in new markets. For instance, we only export our diclofenac produced in ODFs - patch, soft gel, and capsule – to a few markets," explained Luca Crippa, IBSA Farmaceutici's CEO.
The company is actively searching for distributors to licence its products to in both Southeast Asian countries such as Thailand or Vietnam, and in Latin American ones like Brazil or Argentina. IBSA projects double-digit growth in 2021.
Finding the right partner or distributor is even more challenging for more niche companies like Diatheva: "The expansion strategy starts with understanding the challenge. Our kits are very niche and specialized, so we need to screen the different distributors and market agents to identify the right partners for each technology," said Cosimo Lenti, business director of Diatheva.
Working with distributors creates an intermediate cost but covers more geography, factors that need to be balanced. For instance, PharmaNutra estimates that about 65% of its output by unit volume goes into export markets, but because of costs associated with distribution, the value of its exports comes down to represent a third of total revenues. In the future, PharmaNutra plans to maintain its distribution model in smaller markets, but establish subsidiaries in important ones through acquisitions: "The potential of PharmaNutra is gigantic. If we look at our performance in our top 10 markets, it is not a dream to think we can multiply the success in big markets like the US," said Andrea Lacorte, founder and president at PharmaNutra Group.
Many Italian companies have crossed the exports chasm and today their export markets account for more than the domestic ones. Others are at the beginning of this journey. Mastelli, a 70-years old company based in Sanremo, is already present in Eastern Europe, the Gulf countries and Asia, and is now signing new distribution agreements with Germany, France and Spain: "We are proud to be an Italian company, but we believe the future of Mastelli will be not only inside the Italian borders but also in Europe and Asia," said Fabio Fiscaletti, CEO at Mastelli. ■

Paolo Tubertini

CEO,
OLON

> Since the pandemic, we have prioritized imminent health needs and we were able to coordinate with our partners to boost production for some product lines at the detriment of others.

Olon tracks its roots to 1907, but it was 10 years ago that the company was integrated as Olon Spa. Could you share the latest developments?
When I joined Olon at the beginning of the 2000s, Olon's primary vision was to become a leader in the production of APIs and intermediates. Today, we are one of the largest European suppliers of APIs for both the generic and CDMO markets. We are very active in high potency drugs such as cytotoxic substances, as well as antineoplastic compounds, immunosuppressive agents, hormones, antibiotics, and controlled substances. We have 11 manufacturing plants, eight of which are in Italy, one in Spain, one in the US, and one in India.

Olon made a couple of acquisitions in recent years, expanding its footprint in the US and India as well as in biotech. Could you share the strategy behind these acquisitions?
We acquired Infa Group back in 2016, doubling our generics line. Later in 2017, we acquired the Olon Ricerca Biosciences, a centre fully dedicated to R&D that is based in Ohio. It offers world-class contract research and manufacturing services and a broad array of capabilities with an integrated approach to chemical development. In 2018, Olon acquired Italy-based Capua BioServices, a CDMO company highly specialised in microbial manufacturing. Capua BioServices expanded our capabilities in this technology and allowed us to take our offer to the food industry. Finally, we made a strategic acquisition in India to expand our integrated portfolio, services and technology platforms.

What do you think is Italy's competitive advantage as an outsourcing destination for CMDO?
Italy is a leading producer in Europe and the pharma sector accounts for around €33 billion per year, a commensurate figure for a country of our size. Italy offers a rich ecosystem of universities, services, machinery producers, research technicians, analytical labs, all in proximity.

How has Olon contributed to the fight against the pandemic?
We are working as part of five different programs for the development of antiviral drugs. Since the pandemic, we have prioritized imminent health needs and we were able to coordinate with our partners to boost production for some product lines at the detriment of others: When one partner interested in an innovative antiviral API drugs, for instance, asked us to ramp up production at our Rodano site, our other customers showed tremendous understanding and supported us, knowing they can trust us for recouping the volumes when the emergency had passed. Meanwhile, they relied on stock supplies. The industry's synchronic mobilization is an example of global collaboration and solidarity.

What is Olon's current innovation focus?
At Olon, we first look at innovation in terms of innovating the way we make things - our production processes, technologies and market strategies. Within this wider program of innovation, we also see innovation as investing in new technologies, such as flow chemistry, enzymatic production and high potency drugs – a landmark space for Olon, where we have been present for 50 years. Personalized and precision medicine will require smaller drugs and therefore, smaller reactors, which will inadvertently increase prices, so we keep abreast of these developments. In 2021, we foresee a total capital investment of €65 million, which is roughly 12% of our sales.

Olon set out to reduce CO2, GHG, and water consumption by 50% between 2015 and 2025. Could you finalize with a few words on the company's understanding of sustainable growth?
Because we set these targets early on, we are on track to meet them in the next few years. I believe it is important to let our stakeholders know of our commitments to the community and climate. We are constantly committed to reduce the impact on the environment where we operate and to promote a more sustainable API manufacturing approach. We have very aspiring targets to reduce consumption of water and energy, to decrease wastes and carbon dioxide emissions. ■

Giuseppe Allocca

Technical Operations Executive Director,
ALFASIGMA

> We currently have five ongoing development projects in gastroenterology, three of which are already in clinical development, and another R&D project for the treatment of venous and arterial disorders.

Could you introduce Alfasigma to our audience?
Alfasigma is one of the top five Italian pharma companies and number 118 globally. The company was born out of the merger of two main Italian players, Alfa Wassermann and Sigma-Tau in 2015, but the roots of the company date back to 1948. As of May 2021, Alfasigma counts a total workforce of 3,000 people, of which 1,800 work in Italy. Our revenues are proportionally split between the domestic and foreign markets, and our products reach 70 countries, 17 where we have a direct presence through a subsidiary. Alfasigma's 2020 turnover was at over 1 billion €.

What are the main markets where Alfasigma sees opportunity?
We see the US, China and Russia as fast-growing markets where we could further develop, and we are advancing several projects in these countries. Alfasigma produces a blockbuster drug in US and other markets [rifaximina].
US and Europe together account for about 25% of our international sales. In terms of therapeutic areas, gastroenterology is our legacy focus; we have recently acquired the rights to market Lumeblue and bentracimab in Europe and other markets, and we have various products in the pipeline for gastrointestinal and CNS therapeutic areas.

What are the latest R&D developments at Alfasigma?
We are investing in a new R&D facility in Pomezia that we will inaugurate next September; the site is designed to reaffirm our focus on gastroenterology, vascular diseases and neuroscience, but we are also expanding our biotech capacity, looking closer at rare diseases. We currently have five ongoing development projects in gastroenterology, three of which are already in clinical development, and another R&D project for the treatment of venous and arterial disorders. We are also partnering with a number of Patient Organizations, Universities and start-ups – such as the case of NOVAVIDO in Ophthalmology – in order to leverage open innovation and be more and more patient centric.

Alfasigma announced a new leadership model in 2019. What does this entail?
We adopted a new leadership model that seeks to strengthen our governance by prescribing five behaviors: act with team spirit; drive innovation; communicate clearly; do the right thing and more; and provide value for people. Our mission to improve health and quality of life set the basis for everything we do, from R&D to marketing and manufacturing operations, so the five pillars spell out our vision and values in more practical terms for each member of our team with the support of very dedicated management.

Could you share what role does Alfasigma plays as a contract manufacturer?
Alfasigma will never be only a CMO company – we are an R&D-based organization whose growth is leaned towards innovation, but we see an opportunity in the CMO market to put our capabilities to use and gain customers in the medium-to-low volume products of high complexity.

What is your outlook for the Italian pharma industry?
Italy is one of the key pharma hubs in Europe and the growing elder population makes chronic disease management a top priority. The Italian national healthcare system is facing challenges in terms of its long-term sustainability, so the need for affordable treatments will only be growing. Alfasigma partners with pharmacies, physicians, authorities and other organizations to find the right balance in providing affordable drugs.
As we emerge from the pandemic, Italy's post-pandemic recovery plan submitted to the European Union will support the build-back of the economy through strategic investments in digitalization, research and infrastructure modernizations.

Could you share a final message?
As mentioned, Alfasigma is in a transformational mood, a new management has been introduced across our operations and we are inculcating a new culture for the company, preparing for the next big challenge. We'd like to play an even more strategic role in the Italian pharma industry, and we have a very ambitious target to climb up in global rankings from 118 to top 100 global pharma companies. To do so, we expand both organically and inorganically, we invest heavily in R&D, we are recruiting more talent and are engaging partners from all over the world for licensing and acquisitions. ■

Fabrizio Chines

Chairman & CEO,
SIFI GROUP

Our main target is to become a European leader in ophthalmology, so our direct investments will be mostly focused on Europe; meanwhile, we proactively pursue new markets through partners.

Could you introduce SIFI Group?
SIFI has a mission to improve people's lives through meaningful eye care innovation. Dating back to 1935, two pharmacists -one of who was my grandfather - founded the company and it remains headquartered on the slopes of the Etna volcano, in Sicily. Since 2015, mid-size private equity firm 21 Invest has backed us. We are a relatively small company, but despite our size, we have invested significantly in innovation and geographical expansion: SIFI has a direct presence in six countries and exports to 20 markets.

Can you tell us more about your company's international expansion strategy?
We established the first subsidiary in Romania in 1998, and, like with Mexico, these were opportunistic moves to capture two markets that, although small, promised a good balance between sustainable prices and relatively low regulatory barriers. Since having the private equity onboard, we accelerated our international growth by setting up greenfield operations in bigger European markets and making acquisitions to complement our legacy portfolio. Our main target is to become a European leader in ophthalmology, so our direct investments will be mostly focused on Europe; meanwhile, we proactively pursue new markets through partners. For instance, we have a partnership with leading pharma Zydus Cadila to commercialize intraocular lenses (IOLs) in India. Most recently, we entered into a JV with biomed company AffaMed Therapeutics to develop our portfolio of IOLs in Greater China.

SIFI offers both pharma products and devices. Can you walk us through your portfolio and portfolio pipeline?
Innovation has always stayed at the core of our growth: ever since 1989, SIFI was the first to use hyaluronic acid (HA) in artificial tears for dry eye; later in the 1990s, we became pioneers in ophthalmology prescription-based nutraceuticals. Today, we offer pharma products, OTCs, nutraceuticals and devices, but they all follow the prescription-by-ophthalmologist model. In 2020, ophthalmic consultations were reduced, and eye surgeries halved, which affected demand. However, we pushed forward with our innovations: last year, we launched Well Fusion, an innovative technology for IOLs and Synfo, a novel formulation of artificial tears. I'd like to focus on two innovation programs we're currently working on: the first is an orphan drug candidate, Polyhexanide, for the treatment of Acanthamoeba Keratitis (AK), currently at the end of a pivotal Phase 3 study; AK is an ultra-rare disease, a devastating infection leading to blindness or corneal transplant. We should see the readout from our Phase 3 study results in Q3 2021 and then file a marketing authorization application to the EMA. The other program I'd like to point out is the PH007 where we test for a novel mechanism in the treatment of dry eye: this is a topical gel applied on the forehead that will stimulate natural tear production. The program is licensed in from a US-start-up and we have finally started enrolling patients in a dose-ranging Phase 2 study, after a year-long delay caused by Covid.

What are your views on Italy's innovation & investment climate?
As an adviser to venture capital firm Panakès Partners, one of the first Italian funds entirely dedicated to life sciences, I have noticed a positive trend to foster innovation in this space. However, funding for early-stage development remains generally limited, and Italy lags behind countries like France, which sees more liquidity. Pricing and market access are challenging in Europe, and more so in Italy, and this aspect hinders the valuations needed for early-stage programs, even though we have seen some legislative developments to award funds to innovative orphan or oncology drugs. Germany is leading the way in digital therapeutics, devoting a specific budget for these technologies, something which is currently inexistent in Italy. Our country has a great tradition in manufacturing in both APIs and CDMO, moreover, we are attracting more clinical trials, which is another means of localizing investments. Nevertheless, we still have a way to go, especially in terms of regulatory efficiency to increase our Country's competitiveness. ■

International players

ON ITALIAN LAND: THE CASE OF MARKET ACCESS

The third-largest EU country by population after Germany and France, Italy's over 60 million people represent a key market for global pharmaceutical players. Italy also has a very attractive demographic profile, with 23% of the total population aged over 65 and with a life expectancy averaging 83 years, one of the highest in the world. In fact, the number of Italian centenarians has tripled over the last 15 years. These fundamentals render Italy as an important "silver economy," served by all the relevant pharmaceutical and biopharmaceutical global players, including Janssen, Pfizer, Sanofi, Sandoz, Astra Zeneca, Bayer, Baxter, Accord, UCB, Ipsen, AbbVie, Medac, Amgen, Teva, Takeda, Daiichi-Sankyo, and others. 59% of companies active in Italy are foreign-owned, reports Farmindustria.

Despite these credentials, Italy is considered one of the most challenging countries for market access (and price access), with a very complex regulatory roadmap, a cumbersome approval process, difficult negotiations, and a lower price point for reimbursed drugs, especially for generics. This affects both domestic producers as well as international players.

Across Europe, market access is a postcode game. A report published by EPFIA found that newly approved treatments reach western and northern European countries in up to 200 days once market authorization is received, whereas the south and east of Europe wait between 600 and 1,000 days. Italy scored slightly better than the European average, with a 402 days' wait, but remains much behind Germany's 119, Switzerland's 117, or the UK's 209.

Within Italy, however, there are stark differences between its 21 regions. One particularity of the Italian healthcare system is its regional structure and dual governance system, composed of the State and the Regions. The Servizio Sanitario Nazionale (SSN) defines the basic benefit package (livelli essenziali di assistenza or LEA), which covers the majority of reimbursed drugs in Italy. This is controlled by the Ministry of Health, which, in turn, coordinates with the Ministry of Economic Development to set annual budgets. AIFA is the designated drug authority (the equivalent of the US FDA) and the agency responsible for managing pricing and reimbursement. Across these levels, the SSN is organized in 19 regions and two autonomous provinces, each exercising a high degree of power.

This fragmented system, underscored by multiple subsystems, does not only slow down market access but also creates differences across regions. The measures taken by some regions to cut spending have created territorial differences, feeding into a North-South divide. Pharmaceutical companies need to liaise with each region independently, which leads to situations whereby a drug available in one part of Italy could take another six months to be available elsewhere in the same country, wasting crucial patent time.

The interaction and coexistence between these two entities – the State (represented by AIFA) and the Regions – has been a matter of discussion ever since 2001, when AIFA granted more authority to the Regions, and this trend is being reversed. The New Health Pact 2019-2021 approved between the government and the Regions calls for a single

Massimiliano Rocchi

Senior Director Italy and Greece,
ACCORD HEALTHCARE ITALIA

> We play by economies of scale, we leverage our ability to stockpile, and we build good volumes based on forecasts, mechanisms that allowed us to win tender after tender. But the industry cannot continue to reduce the price because margins are already at a critical point.

Could you introduce Accord Healthcare's operations in Italy?
Accord began operations in Europe in 2008, and by 2010 the Italian branch became fully operational; however, it took us two more years to become a truly visible market player. Today, we are a leader for various oncological products in both public and large private hospitals. Adding to our extensive offer of injectable and oral cancer products, over the last five years we expanded our portfolio with numerous chemical entities, but also biosimilars and, most recently, retail products. Having achieved a high market share in the hospital market, we see retail as a new growth space.

How do you think generics companies leverage innovation?
Our tagline, "We make it better," underlines the simple yet difficult task of constantly offering something different and better. The competitiveness of generics companies has been dominated by the lowest price principle, but a new principle started to brew before the pandemic and is becoming increasingly more relevant today: MEAT (the most economically advantageous tender) is gaining momentum as Italy and other European countries faced significant hurdles procuring materials from Asia. The lowest-price model is a very simple adjudication criterion that led to a dependency on the cheapest imported drugs, but the industry needs to move to a different direction, to acknowledge quality and added features. Equivalent drugs can be innovative, and we are very keen to offer competitive advantages that distinguish our products from the rest.

What are the specific advantages that Accord Healthcare enjoys as a vertically integrated company?
We enjoy control at every step of the manufacturing process, which enables us to be a flexible player and fulfil market demand faster. Our bulk production takes place in India, but the drugs are completed at our manufacturing facilities in Europe. Supply chain flexibility has become a must these days. To be able to stay competitive in this context, we need to be very reactive, agile and process more orders.

Could you elaborate on the issue of generics reception in both hospitals and the retail market?
There is a stark difference between the two markets, each entailing its own business model and considerations. In hospital tenders, generics enjoy a very high market share, because any company with the active ingredient in their product can tender, and the lowest price wins, regardless of other criteria. Because of this, the value of hospital generics is low. At the opposite end, generics occupy only about 20% of the retail market, comparably lower to other European countries like Germany or the UK where the market share is somewhere above 70%. Nevertheless, retail generics have a high value of around €2 billion.

As part of your strategy to enter the retail sector, Accord Healthcare has recently launched a new non-medicinal product line called Concquer. Could you elaborate on your strategy in this segment?
Because of our strong presence in oncology, we want to support cancer patients on their journey, and this has translated as offering a full range of support they may request. On top of offering cancer therapies, the new Concquer product line is a range of cosmetic products that may help with the side effects of chemotherapy, tackling issues such as radiodermatitis and other skin issues. We have already launched three products as part of this new line, and more are to come.

Do you have a final message?
As a leader in the tender sector, we are advocating for the MEAT principle, working with stakeholders to implement this concept and replace the price battle. We find ourselves in a vicious cycle – we play by economies of scale, we leverage our ability to stockpile, and we build good volumes based on forecasts, mechanisms that allowed us to win tender after tender. But the industry cannot continue to reduce the price because margins are already at a critical point. We are convinced our products can offer additional features and this amongst other elements should be the winning factor. ■

Luca Crippa

CEO & Managing Director,
IBSA FARMACEUTICI

IBSA has 85 patents on groundbreaking pharmaceutical technology and a portfolio that covers 10 therapeutic areas. We are open to international partners for commercial collaboration and contract manufacturing.

Could you briefly introduce IBSA Farmaceutici?
IBSA stands for Institut Biochimique SA and it started as a small Swiss laboratory in Lugano 40 years ago. IBSA transformed into a global company, active in 10 therapeutic areas with a reach in more than 80 countries. Out of 1.600 people in headquarters, branch offices and manufacturing sites, 600 are in Italy, where we have two production facilities and three R&D centres. IBSA's journey relies on four pillars – People, Innovation, Quality and Responsibility – of which People and Innovation have a central role in our business model: to take generics to the next level, be it by improving their bioavailability, patient acceptance, or easiness to be administered by physicians, patients, or caregivers. People – as employees and as patients - may discard generics as "just generics," but we find tremendous opportunities to innovate in this field. By improving the quality of drugs, we improve the quality of life for our patients.

Could you elaborate on IBSA's key therapies?
IBSA has a vested presence in fertility, including human reproduction and hormonal treatments, such as hormone replacement therapy for sufferers of thyroid issues or other illnesses. We also have a wide portfolio of hyaluronic acid injectable solutions used in osteoarticular therapies – for knees, shoulders, elbows, or other joints. Rather than using genetically engineered microorganisms, we produce hyaluronic acids through biofermentation. We use the same technology in aesthetic medicine.

What are the latest innovations IBSA brings to the market?
IBSA has 85 families of patents on pharma technologies. We collaborated with the University of Milan to work on an orodispersible film (ODF) drug delivery system applied in two molecules: a drug and a food supplement. The first is a medicine used to treat erectile dysfunction. As a dispersible film, the drug dissolves in the mouth without requiring water; it is also easy to carry around as it fits in a wallet and, because it is absorbed at the mouth level, it does not cause stomach distress. The second application of this ODF is for Vitamin D, a globally booming market. Due to the high demand, our production is already at maximum capacity for this product and we are considering production capacity expansions.

What is IBSA's international footprint and what is your expansion strategy?
We have a portfolio of 200 highly innovative drugs that outperform regular generics, but these do not enjoy an even international presence. With our long history in human reproduction, fertility drugs are indeed globally distributed, just as are our aesthetic medicine products. However, IBSA has a much broader basket with a local footprint and we'd like to launch these products in new markets. We produce diclofenac gel in ODFs - patch, soft gel and capsule – that we export only to a few markets. IBSA is actively looking for distributors in both Southeast Asian countries like Thailand or Vietnam, and in Latin American ones like Brazil or Argentina, who could license out our products.
Additionally, we have contract manufacturing capabilities for high-value, quality drugs. It is important to note that IBSA is not a pure CMO ready to produce high quantities at small prices: we are ready to lend our technologies to partners for premium products to increase our asset intensity.

How do you think Italy-made generics are received on international markets?
The "Made in Italy" brand is not a label that speaks of Ferrari or Gucci brands alone; in fact, the Italian pride stands in our high-level technology. Italy is the largest pharma producer in Europe, battling with Germany for this title, but Germany's economy is larger and its population bigger than Italy's by 20 million people. Italy has an ecosystem that enables top-notch quality and consistency. These attributes guarantee a very positive reputation abroad.

Do you have a final message?
When the pandemic started, we gave ourselves three priorities: the safety of our people, production continuity and financial performance. I am happy to say we have been successful in all three, guarding our people's health and not losing a single production day. We closed 2020 with profits and we are poised for double-digit growth in 2021. The future of IBSA is international growth and we invite global partners who share the same passion for quality and innovation to be a part of our success story. ■

Maurizio Sartorato

CEO,
BIDACHEM SPA

> Our working model follows the life cycle philosophy: we invest in innovative products, industrialization of new technologies and in the optimization of our processes to fulfil a sustainable business growth.

Can you introduce Bidachem and explain its position within the Boehringer Ingelheim Group?
Boehringer Ingelheim is an innovative family-owned company with 135 years of experiece. The key to our success is found in the ability to continuously adapt and introduce new products and technologies. The Group, one of the pharmaceutical industry's top 20 companies, operates in three main businesses: animal health, human pharma and biopharmaceutical for contract manufacturing.
As a family-owned company, generations are rooted in our "Leitbild". Embracing sustainable development, social and environmental engagement has always been part of this generational approach and of our legacy.
In the journey towards excellence our "Sustainable Development For Generations" program delivers long-term economic and social value to our patients, stakeholders, employees and the communities that we serve.
Within the Group, Bidachem's APIs cover five out of Boehringer Ingelheim's seven therapeutic areas in human pharma: we produce APIs for cardiovascular diseases (dabigatran), metabolic diseases (empagliflozin, linagliptin), respiratory diseases and oncology (nintedanib) and for immunology (early stage product). Boehringer Ingelheim is also active in CNS and retinal health therapeutic areas.
Our working model follows the life cycle philosophy: we invest in innovative products, industrialization of new technologies and in the optimization of our processes to fulfil a sustainable business growth. In this sense, we act as an internal, special CDMO.

What are the advantages of operating in Lombardy?
Lombardy accounts for over 50% of Italy's total API output. Bidachem benefits from both internal and external competencies, leveraging on a highly qualified workforce thanks to the presence of specialized professional schools and universities, and the support of other companies supplying the latest and most innovative technologies and services. Located in a strategic logistic area, we also have good transport links and excellent access to shipping.

Bidachem continued investments in 2020. Can you share what are these directed to?
Bidachem invests approximately 15 million euros every year for business, safety and sustainable growth – encompassing our people, the environment, and best technologies to improve the cost performance of our products. Over the last 10 years, we invested 130 million euros, and we will maintain the same annual averages to meet the evolving needs of our patients and stakeholders. Specifically, last year we invested in a new line of production for empagliflozin. This investment will amount to 10 million euros and should be completed by 2021. In 2019, we inaugurated a new high containment micronization plant. In addition, in 2018 we invested in a new laboratory for quality control which allows us to provide an additional service to the Group: the analysis and the release of milled APIs manufactured by Bidachem and not only.
Bidachem plays a key role in the supply chain of the Group and our technologies are always updated via transfer of new chemical entities from Boehringer Ingelheim.

Could you elaborate on Bidachem's focus in youth employement and employer mobility?
Boehringer Ingelheim invests in all its employees, especially in young people. The pharma sector is growing, and we must invest in our youth to make sure of the availability of talent in future years. In 2019, Bidachem hired 240 people, a number which will go up to 270 by 2022. We have many young people joining the team, we are working closely with them and foster their skills, especially in management roles.

Bidachem is celebrating its 40-year anniversary in 2021. What are the company's future objectives?
Our aim at Bidachem is to maintain our leadership in engineering, chemistry, quality and safety, by implementing last technologies at our plants, but also leveraging, in future, big data and AI to maximize our performance in terms of quality and costs.
Our efforts are geared towards promoting automation and digitalization, which will allow workers to transit into higher-value positions rather than doing repetitive tasks, better served by a machine. We can make better use of both human and software/ robotic capabilities. Based on variability studies, batches produced in an automated fashion yield more standardized results.
Finally, we are very focused also on sustainability, having recently invested in a new thermal oxidizer at our plant, classified among the best available technologies, ready by the end of this year and which will allow us to further minimize the environmental impact. ■

Italy's health market is very particular due to its federal structure; it is centrally governed, but strong powers are delegated to individual regions. In this sense, the penetration of generics has been slow and differentiated, with higher percentages in the Center-North of the nation.

- Massimo Versace, Country Manager, Sun Pharma

Health Technology Agency (HTA) superseding both the work of AIFA and other agencies in the system. The paper suggested more unity needs to be guaranteed within the NHS. Until this is achieved, international companies need to plan well in advance and deploy an expert regional sales force together with very competent regulatory support.

The negotiation procedure

Charged with finding the right balance between ensuring reimbursement of all essential drugs and keeping costs under control, AIFA finds itself in a difficult position. This balancing act often results in strong downward price pressures affecting pharmaceutical companies. Long and complex, the negotiation procedure between the legislative body (AIFA) and the marketing authorization holder (MAH) often ends on pricing agreements lower compared to other European countries.

The government also imposes expenditure caps on different budgets, with a separate budget for the hospital market and another one for retail. When these thresholds are crossed, 50% of the expenditure is paid back by pharmaceutical companies through a payback mechanism. Stefano Collatina, country lead at Baxter Italy, calls this a hidden discount: "Every year, pharma companies active in the hospital space must accrue the extra money to cover the hidden discount, which makes planning very challenging."

This payback does not apply to orphan drugs and oncological drugs, which are covered by two separate 500 million euros funds. Nevertheless, branded innovative pharmaceuticals in other therapies are affected by the payback, and innovators can think twice before launching their products in Italy. Collatina explained: "Average Italian prices are lower compared to other countries; also, the Italian system is more complicated because in countries like the UK or Germany there is a faster approval pathway and no negotiation. If a satisfactory price agreement for a highly innovative drug cannot be reached with AIFA, the product may well not end up on the Italian market."

Innovative pharma suppliers can also choose to withhold product launches in the country because of the European "referencing system", which allows all regulatory agencies in the EU to see the prices in different countries. Looking at these references, national agencies can start negotiations by requesting a lower-than-EU-average price. It makes sense then for MNCs to begin their product launches with the countries that offer the highest prices before moving down to cheaper markets.

For hospital generic products, prices are settled through tenders rather than direct negotiations. Generics are automatically assigned to the same reimbursement class as the branded drug if the owner can propose a rebate between 30% to 75%. With a highly competitive tender system in place, Italy can secure very high discounts, adding immense pressure on generic players. Giovanni Sala, general manager at Medac Pharma, explained the long-term consequences of a low-price regime: "Due to hindered commercial viability, some products become scarcely available or run out of stock. Unless a different system to reward the value of hospital generic products is brought into place there will be more issues with their availability."

Despite the different measures to contain spending, national pharmaceutical expenditure has been growing over the years, the hospital budget being consistently overrun. Between January-July 2020, the ceiling of total pharma expenditure was exceeded by 16.7%. Hospital spending, in particular, was 2.7 billion euros above the limit. At the end of 2020, drug manufacturers were billed 1.35 billion euros for exceeding the expenditure ceiling according to IQVIA. As a solution to relieve the pressures on both national budgets and pharmaceutical companies, some opinion leaders see the answer in generics: By increasing the share of generics, the government could make savings and use these to reimburse critical innovative drugs.

Drug reimbursement is split under the SNS into two main categories:

Class A) Reimbursed drugs are considered essential and require a medical prescription. This includes hospital products designated as Class H.

Class C) Non-reimbursed drugs are non-prescription drugs, either over the counter (OTCs) or other self-medication (SOP); these are sold in pharmacies, para-pharmacies, or online, and are paid directly by patients.

Stéphane Brocker

Managing Director Italy,
IPSEN

> We are engaging policymakers to overcome existing barriers for bringing innovation into the market and to make the innovation ecosystem sustainable for both pharma companies and public spending.

Can you provide a brief overview of Ipsen's activities in Italy and share some characteristics of the Italian market with our audience?
Reflecting our global focus, Ipsen's key therapeutic areas in Italy are oncology, neurosciences and rare diseases. We have been strengthening our focus in oncology since 1990 and today we have an extensive portfolio for different types of cancers. Our second pillar is dedicated to neurosciences, with a special focus on botulinum toxin to treat movement disorders. We are also developing our activities in rare diseases.
Italy is one of the top five pharma markets in Europe an it has an ageing demographic; this is coupled with a very comprehensive healthcare system that, generally speaking, works well even though it can be slow and lack coordination as the recent pandemic highlighted. One of Italy's particularities which has become very clear during the Covid crisis is the regionalized structure which makes for a very complex market access pathway.

Can you comment on Ipsen's evolving portfolio and current innovation priorities?
Our recent breakthrough innovation includes a treatment for hard-to-treat cancers, used alone or in combination with other innovative molecules.
Pioneering innovations attract the most attention from the public and financial analysts because they significantly improve clinical results or even survival for patients. However, marginal, continuous innovations on existing products are also greatly beneficial for patients and deserve being mentioned. We recently introduced in Italy a long-acting formulation of our product in prostate cancer, a molecule that has been in the market for 30 years – giving patients and healthcare professionals more options to control the condition. We also partnered with patients to identify ways to improve the delivery device of one of our products used in the treatment of neuroendocrine tumors and acromegaly.

How important are digital platforms in the pharma space and can you highlight some of Ipsen's initiatives?
In 2021 we launched "Oltre la Spasticità" (Beyond spasticity), a website designed to help patients, caregivers and the wider public better understand spasticity and how to manage it, covering the whole patient journey from access to diagnosis, treatment, care and expertise.
19% of patients who suffered a stroke develop spasticity 3 months after the stroke episode, and up to 38% patients develop spasticity symptoms a year after the acute event. Unfortunately, it is still often underdiagnosed and under-treated, causing severe disabilities for the patient and impacting strongly on the quality of life of both patients and caregivers.
Thanks to a comprehensive partnership with Patients Associations and interested scientific societies, we developed this platform which includes a list of all specialists and care centers who can help patients understand and manage their symptoms.

What is the significance of the 2020 AIFA pricing and reimbursement update for new drugs?
We must work with the public authorities to redress the short-term budget focus and instead look at long-term KPI indicators and the impact that a new drug will have in a 10-years timeframe to create a more comprehensive value package for new innovations. Taking a multi-stakeholder approach, I believe we can reach a sustainable market scenario for Italy.
The new law introduced in 2020 for pricing and reimbursement came with various challenges. The initial objective was to increase transparency but by making the process more burdensome we fear it may further slow access to innovation in Italy. The new law requires AIFA to renegotiate pharmaceutical products every two years. We think this will create an unnecessary burden and excess workload for AIFA and may negatively impact innovation as our sector needs a predictable and stable environment to operate.

Ipsen Italy was awarded for "Best workplace for women". What has earned Ipsen this award?
We are proud of this award especially since it is based on the genuine feedback of our employees within a survey carried out by the Great Place to Work Institute Italia.
This is the result of a long-standing commitment to make Ipsen the best possible place for everyone. We value talent and diversity, regardless of age, gender, sexual orientation or ethnicity.

What are Ipsen's key priorities in the next 2-3 years?
Our goal is to continue bringing new assets of real and added value to patients. We are also engaging policymakers to overcome existing barriers for bringing innovation into the market and to make the innovation ecosystem sustainable for both pharma companies and public spending. ■

Federico Chinni

CEO & Managing Director,
UCB

> **Our multi-year collaboration with Microsoft combines the capabilities of our scientists with computational services, data and AI.**

UCB is one of the largest European biopharma companies. How important is the Italian branch?
Italy is one of the top five European markets for UCB. Headquartered in Milan, UCB Italy hires 140 employees, while at the beginning of 2020, we were only 102 employees, having grown substantially this past year. This growth is underpinned by our ambitious plan to launch six new products in six years.

How is UCB's therapeutic focus evolving?
UCB is focused on two main therapeutic areas: immunology and neurology. However, we are supporting an important continuous growth campaign through expansions. For instance, we are investing on the PSO (psoriasis) dermatological space through a new extremely promising molecule. For osteoporosis, we are also bringing to the market an injectable able to finally provide some innovation in this area after years. Also, UCB is complementing the portfolio of chemical drugs with new therapies, including gene therapy. As an example, in the neuro-inflammation field, we take a special interest in myasthenia gravis, a rare neurological disease.

UCB and Microsoft entered a collaboration to accelerate drug discovery and development. How do you see the importance of AI in pipeline development?
Our multi-year collaboration with Microsoft combines the capabilities of our scientists with computational services, data, and AI. AI can manage and corroborate huge data volumes, especially coming from clinical trials, which speeds up the discovery process. Secondly, AI enables much closer customization to factors such as gender, a key element in developing precision medicine.

UCB uses telemedicine to connect with epilepsy patients. How is digitalization shaping patient-doctor-pharma interactions?
UCB has a strong legacy in the epilepsy market, and I strongly believe in the possibilities that digital can bring. Both the Italian government and the EU are also prioritizing this aspect of healthcare: an important focus of the 20 billion euros PNRR (Italy's recovery fund) in reshaping healthcare will be that of telemedicine with the goal that the medical needs of over 10% of the over 65 years' old can be attended through telemedicine by 2026. As a company, we don't only support this broader plan, but we also support an app for care, seeking to empower patients to register symptoms - just like they would in a diary - and to connect within a consultation. The first part of any doctor visit is filled with administrative tasks, so by registering drug history or symptomatology through the app, the consultation time can be more effectively spent. The pandemic is a chance to design a better normal rather than a new normal, and digitalization is surely part of this.

What is UCB's approach to sustainability? How are your climate efforts translated at a local level?
Globally, UCB invests about 30% of our turnover back in R&D, in the hope we can impact society by answering unmet medical needs. In terms of climate actions, we have very clear, science-based targets for the next decade, against a 2020 benchmark: to reach carbon neutrality, to reduce water consumption by 30%, and to curb pollution by 25%, all by 2030.

Italy has one of the world's oldest populations. How does this impact the focus of the industry?
Italy is a very interesting ecosystem for what's been named "the silver economy." With the world's second-largest share of people aged 65 and over (after Japan), prevention will be critical to ensure continued wellbeing, but also the country's budgetary sustainability. In the long-term, a higher geriatric percentage puts increased pressure on the economy, but also on healthcare, especially in a public healthcare model. More focus on prevention, healthy lifestyles, and potentially curing therapies like gene therapy will be fundamental.

What are your main priorities in the medium term, and what is your message to our audience?
UCB has three key priorities: The first one is to become the preferred biopharma company in Italy through our patient-centric services via a concept of connected healthcare: We seek to put patients at the same decision table with other stakeholders for decisions regarding their therapies. Secondly, we want to stand out as an innovative and digital player. Finally, UCB wants to be known for its sustainability efforts. To be successful in the future, we need three key characteristics: resilience as a team, agility (and moving fast with the market), and diversity to embrace different perspectives. ■

Paradoxically, Italy is the largest generics market by value, but we have the lowest prices. Unsustainable in the domestic market, Italian generics leveraged export markets. Once again, this can lead to domestic product shortages, even if Italian-based plants work at capacity.

- Stefano Collatina, Country Lead, Baxter International

Equivalent drugs

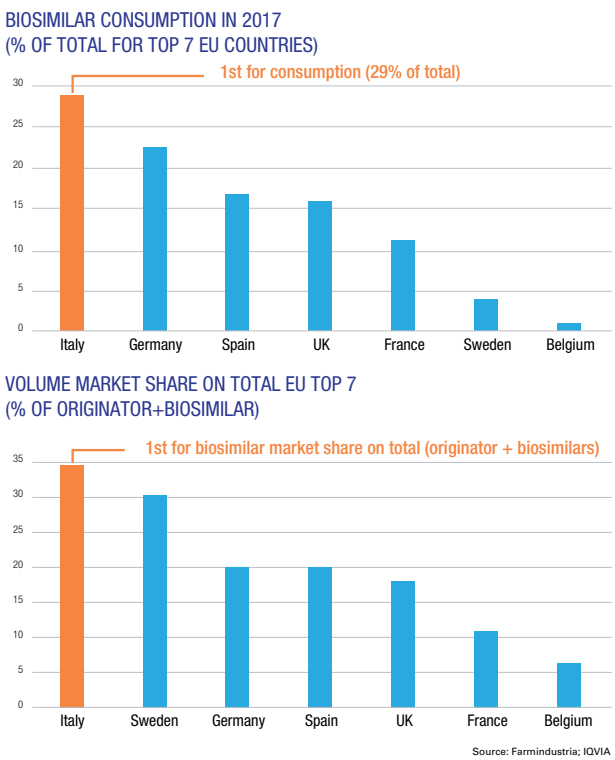
Equivalent drugs - including generics, biosimilars, and value-added medicines (VAMs) – form a very peculiar landscape in Italy. While generics have the lowest penetration rate in Europe, biosimilars enjoy the highest. Generics came later in Italy because the country only introduced the patent law in 1998, 20 years later compared to Germany, for instance. By that time, many patents had already expired.

There are big discrepancies between the hospital and retail segments, since doctors are more likely to choose the cheaper, generic version, while consumers buy more based on brand preferences. This explains why biosimilars, which are typically specialized drugs handled by doctors, represent a high share of about 30% in the hospital market.

The hospital and retail channels for generic drugs also have different business models, explained Massimiliano Rocchi, senior director at Accord Healthcare Italia: "In hospital tenders, generics enjoy a very high market share because any company with the active ingredient in their product can tender, and the lowest price wins, regardless of other criteria. Because of this, the value of hospital generics is low. At the opposite end, generics occupy only about 20% of the retail market, comparably lower to other European countries like Germany or the UK where the market share is somewhere above 70%. Nevertheless, retail generics have a high value of around 2 billion euros."

Nevertheless, the expiration of many blockbuster drugs over the past decade has given a boost to both generics and biosimilars, while market uptake is growing. "Luckily, today the 'generic culture' has taken root both among citizens and pharmacists. Until a few years ago, there was a certain distrust in the clinical world among GP and specialists, but this is being overcome. I believe that we are moving towards a positioning of the generic which reflects the situation of the other major European countries," said Massimo Versace, country manager at Sun Pharma (NSE: SUNPHARMA).

Biosimilars Consumption in the EU by volume



Source: Farmindustria; IQVIA

This cultural shift may also drive change at the policy level. The pandemic reiterated the importance of generic products. In Italy, 70% of the products used in acute therapies, including antibiotics or anti-infectives, are generics, informed Enrique Häusermann, president at EGUALIA, the association representing the equivalent market in Italy. Häusermann observed that the industry's struggled to meet demand at the height of the pandemic, which raises questions about the future: "Without added capacity in key areas like liquid and powder injectables, which are more difficult to produce in large volumes, our ability to meet future demand is put into question," he said.

The pandemic also called into question the pricing model that favors the cheapest drugs, which are typically imported. With prices dropping tender after tender, Italy must revisit its price model. Today, competitiveness in the generics space is largely determined by "the lowest price," but companies like Accord are calling for a different approach based on the "most economically advantageous tender" (MEAT): "The lowest-price model is a very simple adjudication criterion that led to a dependency on the cheapest imported drugs, but the industry needs to move to a different direction, to acknowledge quality and added features," said Massimiliano Rocchi, senior director at Accord Healthcare Italy.

Defined as the opposites of "originals," generics are marked by an underlying perception that they cannot be innovative. However, original and generic drugs can also be seen as part of a continuum, each playing key roles in the market. Often, a generic goes beyond copying a branded drug and

can offer added features in terms of patient compliance, accessibility, bioavailability, administration, or even improved shelf life and sustainability. In recognition of these evolving complexities, the country's association representing equivalent drugs changed its name from Assogenerici, a name which only made reference to the classic generic drugs, to EGUALIA. The new name emphasizes a stronger focus on equal access to health enabled by equivalent drugs, but it also encompasses a broader range of products, including biosimilars and value-added products (VAMs). VAMs are products that offer additional benefits such as higher-dosage concentrations or a novel delivery system that increases compliance. "VAMs contribute to addressing unmet patient needs. Moving from a one-size-fits-all to a much more tailored and patient specific approach, VAMs are one of the key components of the customization of healthcare," said Enrique Häusermann, president of EGUALIA.

The centrality of "added value" resonates with AIFA's new degree which places greater focus on the therapeutic value of each drug. Pharmaceutical companies starting reimbursement negotiations will need to show the possible added therapeutic value of the new drug compared to other treatments on the market. The 2020 decree is a modification to the 2001 law and comes with different reforms, including a simplification of the requirements for biosimilar reimbursement. Though these reforms should bring some relief to the industry, they also raise concerns. "The initial objective of the new law introduced in 2020 was to increase transparency but by making the process more burdensome we fear it may further slow access to innovation in Italy," said Stéphane Brocker, managing director, Ipsen Italy (EPA: IPN). ■

In 2021, we are not only celebrating our 75th anniversary as a group, and also 25 years since the Origgio plant plant became part of Grünenthal Group. The site produces solid pharmaceutical forms and small volume liquids, as well as offering biopharma packaging, pharma development, and lab services. We recently updated our infrastructure to 1,600 cold storage pallet places.

- Aldo Sterpone, General Manager, Grünenthal Italia

Enrique Häusermann

President,
EGUALIA

> The NHS must navigate a very fine balance when putting high pressure on hospital drugs at the risk of ending up with product shortages.

Assogenerici was rebranded "Egualia" in October 2020. What led to the name change?

"Assogenerici" captures the name of 'association for generic products,' but this name no longer covered the full spectrum of our focus. Originally, the association represented generics producers, but in the last 10 years, we incorporated companies producing biosimilars, and more recently, value-added medicines. Therefore, we shifted to a more inclusive name. Egualia - Industrie Farmaci Accesibili, implies greater accessibility and universality, both in terms of products and from a social point of view.

How has the Italian generics industry navigated the pandemic?

Around 70% of the products used in acute therapies are generics, so between March and May 2020, our manufacturing industry faced the great challenge of raising production rates to meet inflated demand. This was made possible by employees who continued work in the plants despite the risk of infection. But we must think seriously about the future because, without added capacity in key areas like liquid and powder injectables, which are more difficult to produce in large volumes, our ability to meet future demand is put into question. Italy must invest in high potency drugs especially in oncology and hormones to maintain its competitiveness in Europe and keep up with demand.

Could you share with our audience the context for generics acceptance in Italy?

The Italian generic market had a late start compared to other European countries, which partly explains its lower uptake. Generic companies came to Italy 20 years later compared to other countries and after the expiration date of many patents. Furthermore, there have been fewer incentives for Italian generics unlike in other countries. In the last 10 years, however, the generic market has been growing faster because of the wave of patent expirations in many blockbuster drugs.

Conversely, biosimilars take a bigger market share in Italy, of approximately 30% by volume and 15% by value. Biosimilars are also directly connected to specialists, who understand better the concept of bioequivalence above other perceptions. This is a continuously growing market.

How do you think generics companies in Italy could better tackle the tight price environment and reimbursement system?

We must make a distinction between primary care products and hospital products. Primary care products have suffered a substantial price reduction imposed by the NHS, but these players can survive as they rely on volume. However, hospital products – many of which are generics – are supplied through tenders, and tender prices continue to drop. If this trend persists, companies will no longer be interested in marketing their products in Italy, which affects not just the pharma industry but patients themselves. The NHS must navigate a very fine balance when putting high pressure on hospital drugs at the risk of ending up with product shortages. The situation is different for patented products, where there is a significant over-expenditure.

Could you comment on the recent degree announced by AIFA?

Despite the complex situation of the last 10-12 months, we have seen positive regulatory developments. An important milestone is solving the payback system which was introduced as an emergency tool in 2012. There is a growing gap between over-spending for hospital products and left-over budget in primary care. In the past, the payback system was based on growth, while now, it is based on market share, which avoids legal discussions between pharma companies and AIFA. AIFA also simplified the negotiation procedure for patent products, making the process faster.

Do you have a final message for GBR's audience?

Our members are currently in good health. However, Italian manufacturing businesses need simplified approval procedures, because they have to comply with both European and local rules. MNCs are more interested in countries like Germany because there they can obtain authorization for one year of production faster and they can cash in more revenue.

We learned in 2020 that pharma companies and authorities can work together to speed up the authorization process and find solutions for the fast import of APIs. The pandemic demonstrated that approval procedures can be simplified, and we ask for the same system that was applied during the crisis to stay on in the future. ■

Contract manufacturing and APIs

ONSHORE: ITALY'S COMPETITIVENESS

The pandemic has encouraged the debate regarding the reshoring of pharmaceutical production, which could accelerate the sector's growth significantly in Italy, as well as in the rest of Europe and in the US. However, this depends greatly on the policies of each country. Large-scale investments surely need the encouragement of political action and political clarity.

- Pierfrancesco Morosini, CEO, Icrom

The emergence of contract (development) and manufacturing organizations (CDMO/CMOs) is an indication of the globalization of the pharmaceutical industry. Drug companies outsource their production to third-parties, often offshore CDMOs, in the pursuit of greater profitability; this way, they also outsource the many challenges that come with drug manufacturing, which is capital intensive, highly regulated, as well as requiring specialized customizations. On the back of these factors and accentuated by the higher demand for acute therapies in 2020, the global CDMO sector is expected to grow at 6.5% CAGR over the next five years, according to Reportlinker.

Driven by a strong export vocation, but also helped by a mix of lower production costs combined with highly skilled professionals, Italy's CDMO industry has been growing uninterruptedly since 2005, making the country a European leader in toll production. The market is composed of about 150 players, half of which are API producers, while the other half is represented by pure CMOs, excess capacity CMOs (pharmaceutical companies with their own proprietary molecules who also offer toll production), as well as packaging and other support service companies supplying to third parties. Well-known local players include Olon Spa, BSP Pharmaceuticals, or Fabbrica Italiana Sintetici (FIS). These are joined by foreign names such as Recipharm, Patheon, Teva, Cambrex and Corden Pharma. The majority of Italy's CMDOs are based in Milan and the broader Lombardy region.

While finished dosage forms (FDFs) producers experienced demand imbalances in their portfolios, most CDMOs were able to grow in 2020 because they had the flexibility to switch to essential Covid-related therapies. To channel their resources to acute, in-demand therapies, CDMOs and API producers collaborated with their customers. Olon, one of the largest European API producers, re-prioritized production at its Rodano facility in response to the emergency: "When one partner asked us to ramp up production for an innovative antiviral API drug, our other customers showed tremendous understanding and supported us, knowing they can trust us for recouping the volumes when the emergency had passed," said Paolo Tubertini, the CEO.

If demand wasn't the biggest problem, API producers came face to face with another issue that had been preoccupying the industry for a long time, namely the country's reliance on imported raw materials and excipients used in the production of APIs. While Italy produces about 9% of the world's APIs by value share, India and China are the de facto leaders in both APIs and component materials globally. Paolo Russolo, the president of Aschimfarma – the association representing the API and intermediates producers in the country

Paolo Russolo

President,
ASCHIMFARMA – FEDERCHIMICA

Companies invest heavily in maximizing efficiencies and introducing new production techniques. The sector invests 3% of its turnover in applied research and 10% in plant optimization.

Could you remind our audience of the main mandate of Aschimfarma?
As part of the Italian Federation of the Chemical Industry (Federchimica), Aschimfarma represents the manufacturers of APIs and intermediates for the pharmaceutical and biotechnology industries. The sector is made of about 72 companies with 109 production sites, and it accounts for a turnover of €4.3 billion – this is approximately 9% of the world's market. 11,900 people work in this sector. The API industry in Italy is very export-oriented, 90% of the total value being represented by export markets, of which 46% goes to Europe. We are open for dialogue with authorities about how we can promote Italy's pharma leadership on the world stage.

Italy's APIs industry is the largest in Europe. What are the industry's main strengths?
To start with, companies invest heavily in maximizing efficiencies and introducing new production techniques. The sector invests 3% of its turnover in applied research and 10% in plant optimization. Skills also represent an important competitive advantage: with labor costs exceeding the manufacturing average by 50%, the level of qualifications and professionalism is very high. Compared to other manufacturing industries, the number of R&D staff is twice as much in the pharma sector. Italy is recognized as a centre of excellence for research, technology and quality. Finally, our companies leverage on long-term relationships of trust with customers from around the world.

How has the pandemic affected the API sector in Italy?
The chemical pharma sector grew in 2020, at a time when the chemicals and other industries suffered big declines. The COVID-19 emergency highlighted the vulnerability of the European drug supply chain, which sources 74% of its starting materials and intermediates supplies for API production from Asia. This problem preceded the pandemic, and was accentuated by site accidents and factories' shutdowns in China and India in recent years. The pandemic further exacerbated the risks that the European health system is exposed to in a highly globalized and complex pharma supply chain. Whereas we can synthesize drugs in Europe, raw materials are no longer manufactured here.

How do you think Western pharma producers can mitigate raw materials dependency on Asia?
The need to have a robust and autonomous pharmaceutical supply chain is evident for all countries: China, the United States, India, Japan, France have already launched measures to make their supply chains more extensive and more sustainable. Europe's health autonomy will largely depend on its ability to maintain and develop its existing industrial base, as well as to invest in innovative and sustainable technologies. API producers are ready to accept this challenge, committing to work with the European Commission in order to create the best conditions to consolidate the pharmaceutical supply chain. Italy is able to supply, with the help of other European manufacturers, about 90% of all European molecules, but this would require a massive simplification of national regulatory systems in target countries. I am optimistic about the future of the Italian API sector and the medium-term forecast is positive.

What are the most significant trends and regulations shaping the industry?
There are various concrete initiatives at European and Italian level that go in the right direction. At the European level, the Pharmaceutical Strategy, communicated on 25 November 2020 and launched as "The EU Pharmaceutical Structured Dialogue" on 26 February 2021, is rolled out across 4 workstreams: definition of robust supply chain; causes and drivers of vulnerabilities and dependencies of supply chains; critical medical products; and innovation. Driving this strategy in Italy, the National Technology Cluster Life Sciences (ALISEI) is running a project for the "Reshoring of pharmaceuticals and active pharmaceutical ingredients in Italy." Some companies have already presented detailed development plans that are currently under examination by the Italian authorities.

How do you perceive the Italian regulatory framework for the API industry?
In order to simplify the regulatory system, we must accelerate the authorization processes for APIs and medicinal products. We also lobby for the global harmonization of the regulations across three dimensions: quality, safety and the environment.

What are Aschimfarma's priorities moving forward?
Our main agenda is to simplify and speed up the authorization process, identify the essential APIs that are at risk of running short, help secure better return on investment for the industry, and harmonize GMP and environmental inspections between European and non-European manufacturers. ■

Aldo Magnini

Managing Director,
CAMBREX

> As a specialist in generics, we must constantly improve the chemistry of the drugs that touch different therapeutic areas.

Could you give us a brief history of Cambrex?
Cambrex was founded in 1981, and by 1990, it was listed on the NYSE. A couple of significant acquisitions followed since, including the Salsbury Chemicals plant now called Cambrex Charles City, and internationally, the acquisition of the Swedish plant in Karlskoga and the Profarmaco plant in Italy. A more recent acquisition is the buy-out of High Point in 2016, as well as FDFs facility Halo Pharma in 2018 and analytical-services firm Avista Pharma Solutions in 2019.

Can you introduce Cambrex Italy and your capabilities at the Paullo facility?
Cambrex Profarmaco Milano dates back to a company born in 1946, which became part of Cambrex in 1992. The Paullo site is close to Milan, and we are a team of 312 people operating a five-day/week, three-shifts/day manufacturing plant. 95% of our business is represented by generic APIs. Every year, we invest about 8 million euros, and in the last few years, we have allocated this investment to the construction of a new laboratory. We have 34 people dedicated to R&D, and they come up with 3-4 new active ingredients annually – which they develop all the way to submitting the master file to AIFA. Currently, we have over 70 drug master files in different therapeutic areas, including controlled substances like benzodiazepine, a tranquilizing compound. In the context of the pandemic, this type of compound was particularly important for hospitals that treated Covid-patients.

What is your investment focus?
As a specialist in generics, we must constantly improve the chemistry of the drugs that touch different therapeutic areas. Anti-cancer therapies with high potent drugs, or metabolic drugs for the treatment of diabetes, for instance, are very central in today's market. Our technology evolves to follow these markets. Specifically, we invested in highly potent compounds to adhere to a market trend of using lower dosage – higher potency drugs. We also invested in a flow reactor to improve productivity and reduce the risk of a hazard reaction at high temperatures. This type of technology is required by some new chemical entities under development by Big Pharma, so we adapted and implemented this technology not just at a lab scale, but at an industrial scale.

How do you observe the trend of localization as a result of the pandemic?
There is indeed a tendency to regionalize or localize production as a reaction to the supply chain angst created in 2020. In the US, there have been initiatives – preceding the pandemic – to create complete supply chain lines in the country, but this trend will vary in each country. China too has been strategizing around creating more autonomy in terms of its supply. However, I think that if the policy does not change in the coming years to support this de-globalization trend, we will be seeing a return of the typical industrial organization that relies on foreign imports.

What are the most interesting markets for generics?
The generics business reflects the most interesting markets for pharmaceuticals generally, and these have consistently been represented by the US, Europe and Japan. At the same time, Far East countries like Korea, Indonesia, China and India are becoming increasingly more important. Cambrex enjoys a strong position in the US and Europe, and we already registered some master files in China, whereas in Japan we have 26 registered master files. Finally, the former Russian Republic is also gaining attention.

What are Cambrex's key strengths in the competitive API and CDMO business?
The costs gap between Western and Asian producers remains accentuated, so as a US-based CDMO, our strategy is to differentiate through premium quality, using the most advanced technology and developing complex chemical products. We are leveraging the premium concept above cost competitiveness. I believe customers are becoming more concerned with having a reliable partner that passes all compliance points required by health authorities, and who can guarantee risk-free supply. Cambrex follows closely each regulatory development, and our most important asset remains our people. They are the ones who ensure the highest standards of quality, so we seek to create value through our human resources. In Italy, we have had a very low turnover of just 3% in the last 20 years. ■

Pierfrancesco Morosini

CEO,
ICROM

> **Icrom has seen a transformation of our model from a pure API manufacturer into a CDMO with the capacity to work on the development of complex and new APIs, especially those used in clinical trials.**

Can you introduce Icrom to our international audience?
Icrom is an Italian CDMO leader for the production of APIs and GMP intermediates. We also provide high-tech services for the development of chemical processes. The company was founded in the 1960s by a French entrepreneur, and in 1996 it was acquired by a group of companies called Proxis Développement. Since then, the company started experiencing high growth and made several substantial investments. For instance, in 2018, we opened a new R&D center and in 2020, we completed the construction of a new and larger warehouse and a Quality Unit building including state-of-the art QC labs .

Could you highlight some recent milestones?
In the past, Icrom was exclusively recognized as a generic API manufacturer. The company has seen a transformation of our model from a pure API manufacturer into a CDMO with the capacity to work on the development of complex and new APIs, especially those used in clinical trials. Over the last 10 years, we have made important investments to sustain this transition. Earlier this year, we started building a GMP "clinical-scale-API" manufacturing facility, which will be fully dedicated to CDMO activity.

Can you elaborate on the significance of your R&D center and explain how it has boosted your capabilities?
The new R&D center allows us to concentrate more expertise by bringing in a higher number of scientists. Moreover, this expertise is supporting our consolidation in different specialties, such as biocatalysis, flow chemistry and high-potency APIs, including ADC. By investing in this new R&D center, we are expanding our scope and keeping up with the latest technologies, future-proofing for what is becoming a much more complex and dynamic field. We see the market approaching increasingly more complex molecules to tap into unmet medical needs, so we must be prepared to respond to complex chemistry.

What is Icrom's international footprint and what is your strategy for further expansion?
Icrom has a presence already in 40 countries. Historically, we have been strong in regulated markets such as Europe and Japan, and our aim is to gain more market share in North America. For this reason, we are targeting biotech companies as our preferred clients and we are developing capabilities and services to clinical APIs, particularly high-potency APIs. The US is the world's biggest center for pharmaceutical research, with outstanding hubs like San Francisco and Boston. We are actually looking to acquire a manufacturing site devoted to clinical APIs in one of these areas to be closer to our US clients in the future. This would be our second manufacturing site and the first outside of Italy.

What are the main trends that are shaping the industry today?
The Italian pharmaceutical industry is seeing great hype at the moment. Throughout the years, Italy has been able to develop special technologies for the production of APIs and finished dosage forms, positioning itself as a manufacturing and export leader, as well as a center of excellence for specialty pharma production, including biosimilars and high potency drugs. The pandemic has encouraged the debate regarding the reshoring of pharmaceutical production, which could accelerate the sector's growth significantly in Italy, as well as in the rest of Europe and in the US. However, this depends greatly on the policies of each country. Large-scale investments surely need the encouragement of political action and political clarity.

What are Icrom's main objectives in the medium term?
Icrom aims to become a key hub for specialty API production services not only by internal growth, but also through partnerships and acquisitions. We are building a network of strategic partners that we can turn to and complement our own service offering. Our goal is to become a boutique one-stop shop, where clients can find high-tech services and capabilities. The company and the Proxis Group are enjoying a high growth, and we expect to reach a turnover of around €200 million by the end of 2021 with further growth in 2022. Indeed, despite acquisition plans being put on hold due to the inability to travel and the difficulty of closing a deal remotely, our optimistic projections would see us making a transaction in a year's time. ■

– told GBR that 74% of the country's raw materials and intermediates come from Asia.

This exposes a much bigger global issue. Dictated by the same principles of profitability and globalized production, most pharmaceutical companies have outsourced their ingredients supply to low-cost countries, which has led to very intricate supply chains and dependencies. Concerns over the quality and sustainability of these materials have been smoldered over the years, but the pandemic brought the issue into close focus. "The CMO business has been challenged due to national border and movement restrictions since we depend on other countries to source raw materials used in injectables. To manage this scenario, it's very important to have a really flexible manufacturing and technical organization," said Giovanni Mariani, the CEO of Lisapharma, an Italian company dating back to 1925 and specialized in injectable products, for both direct sales and as a contractor for domestic and MNC pharma players.

At the European level, there is a clear argument for building resilience against external shocks, but there are no actual relocation policies debated. In EU phrasing, the term "health sovereignty" has started to appear alongside the more benign "resilience," but the bloc is careful to make the difference between autonomy and protectionism, the first being justified by a need to protect European values, including quality and sustainability, and the second directly contradicting other core values, such as market openness and free trade. It would be naïve to think that entire supply chains can be recreated, and papers like the EU Action Plan on Critical Raw Materials rather suggest the diversification of supply chains as well as investing in European-based strategic production assets.

Italy is conducting these EU discussions locally. The national Advanced Life Science Cluster (ALISEI) is driving a project called "Reshoring of pharmaceuticals and APIs in Italy" as a continuation of the "EU Pharmaceutical Structured Dialogue" launched in February 2021. The dialogue initiative has four workstreams in sight, including creating a more robust supply chain, identifying vulnerabilities and critical products, as well as innovation and modernization.

Italy together with other European producers could cover 90% of the continent's API needs, believes Paolo Russolo, the president of Aschimfarma, but this would require big policy changes: "If the policy does not change in the coming years to support this de-globalization trend, we will be seeing a return of the typical industrial organization that relies on foreign imports," he said.

Leveraging Quality

Even without an explicit regionalization policy, the competition criteria between Italian and international CDMOs have changed since the pandemic, evolving from a mere price comparison to more avid considerations of quality, safety and sustainability. Russolo hinted at the lack of regulatory standardization, given that Italian APIs adhere to strict European requirements whereas products made outside of Europe are GMP certified by their respective licensing country. Even though Italian API and CMDO producers remain dependent on raw material imports, they can leverage quality, green production, and high-tech to differentiate in the competitive market. According to Aschimfarma, the API industry invests on average 3% of its turnover in applied research and 10% in plant optimization. These investments keep up with a fast-moving pharma market and its ever-more complex, more personalized, higher-potency, lower-dosage, and varied formulations. For example, Cambrex (NYSE: CBM), a CDMO producing generic APIs, comes up with three to four new APIs, including controlled substances like benzodiazepine, each year. Every year the company invests about 8 million euros in the Italian site.

To support the development of complex chemistry, CDMOs also invest in equipment and production processes. Olon, for example, is investing in flow chemistry and enzymatic production, in anticipation of higher demand for personalized and precision medicine. The company allocated a capital investment of US$65 million in FY2021; 12% of its total sales.

Companies are also paying attention to automation and digitalization. "Automation and digitalization will allow workers to transit into higher-value positions rather than doing repetitive tasks, which are better served by a machine. Based on variability studies, batches produced in an automated fashion yield more standardized results," said Maurizio Sartorato, the CEO of Bidachem.

Cosimo Lenti

Business Director,
DIATHEVA

Diatheva specializes in the field of diagnostic kits but, above all, we offer CDMO services regarding the GMP production of biopharmaceutical active ingredients.

Can you introduce Diatheva and its position within SOL Group?
Diatheva was founded in 2002 as a spin-off of the University of Urbino, in Italy, and in 2012 it was acquired by SOL group. Diatheva is part of the Biotechnology Division of SOL Group, a global leader in medical gases that in the last ten years started differentiating its activities and investing also in the biotech field. SOL group 2020 revenue was about €1 billion. Diatheva specializes in the field of diagnostic kits but, above all, we offer CDMO services regarding the GMP production of biopharmaceutical active ingredients. By collaborating with both private and public entities, our mission is to bring research into application. We work in synergy with the other SOL biotech companies – CryoLab and Personal Genomics.
We are well positioned to provide support at all stages of the biopharmaceutical process development, from small scale to large production. In our state-of-the art GMP production facility authorized by EMA we produce and release biological APIs for preclinical and Phase I/II clinical trials. Our R&D department and university R&D labs together speak the same language and we leverage our development and industrialization resources to turn their ideas into a successful product.

Can you elaborate on how Diatheva leverages synergies with Personal Genomics and CryoLab?

Personal Genomics and Cryolab are service provider companies. Personal Genomics is specialized in sequencing and genetic services, CryoLab in bioshipping, cryorecovery and cryobanking. To give an example of an existing synergy, since the beginning of the pandemic, Personal Genomics was accredited by the Italian Ministry of Health for the COVID-19 PCR analysis by using Diatheva PCR kit. In addition, Personal Genomics is playing a key role in the sequencing of samples in order to identify the virus variants. Cryolab, on the other hand, offers cryobanking services of positive samples that require appropriate storage and it is also involved in the transportation and logistics of the COVID-19 vaccines. It is such synergies we seek to develop further from here on.

What are Diatheva's current R&D projects?
One of our current most important R&D projects focuses on woman's health and consists in the development of a new diagnostic kit for endometriosis. This is a pathology that affects 10-15% of women of reproductive age and the percentage increases to 30-50% in case of women with difficulties in conception. Its diagnosis is a long and invasive process that usually takes years. In collaboration with the inventor Prof. Signorile, who is the President of the Italian Endometriosis Foundation, Diatheva is industrializing a kit based on innovative biomarkers that can be easily identified starting from a saliva sample.
We have our own research and development of three novel biologic therapeutics in the oncology and infectious diseases areas.

As an actor in biotech and supplier of bio-APIs, how are you seeing demand in this segment?

Looking at the global picture, the biotech sector is estimated to reach USD 950 billion in revenues by 2027, according to Global Market Insights. The pandemic has unlocked the necessary investments that will fuel the industry's growth. The pandemic has also revealed few gaps; we all became aware of the necessity to increase manufacturing capabilities during the rush for sourcing the COVID-19 vaccines, which should encourage more fervent fund allocations in the years to come.

What is your main internationalization strategy?
My responsibility is to build a global distribution network, by promoting the Diatheva brand. Our current geographical footprint is mostly in EMEA. The expansion strategy starts with understanding the challenge: our kits are very niche and specialized, so we need to screen the different distributors and market agents to identify the right partners for each technology. SOL group is globally present on different continents and they can facilitate logistics, transportation and administrative aspects which are subject to country dependent regulations.

Do you have a final message?
Diatheva promotes biotechnological innovation by providing high-value customized diagnostic kits and solutions to laboratories that operate closest to the patient. Now, more than ever, the public opinion also knows about the importance of investing in innovative technologies. Diatheva can play an important role in the field of scientific innovation at an international level. ■

Dominating the Italian CDMO sector, medium-sized companies have superior flexibility and are able to constantly innovate and introduce new technologies. However, reducing bureaucratic procedures and adding incentives through fiscal benefits will help CDMOs to invest more in new technologies, drug development and digitalization.

- Rocco Pavese, CEO, Genetic

Bidachem belongs to the top 20 global pharma company Boehringer Ingelheim Group and produces APIs in five therapeutic areas for the Group. Every year, Bidachem invests about 15 million euros in Italy; in recent years, it added a new empagliflozin production line, as well as opening a high containment micronization plant and a new quality control lab.
These unusually high levels of investment have allowed Italian players to become very specialized. As an example, Valpharma, an Italian CDMO which is also putting about 10% of its revenue into R&D every year, offers niche, modified-release technologies applied to pharmaceuticals, nutraceuticals, medical devices, hand sanitizers and, most recently, complementary feeds in the veterinary space. By continuing to improve its technology the company has grown by expanding horizontally into different segments and is preparing for the next challenge, in biologics. "Monoclonal antibodies and vaccines are now taking the place of classic solid oral products that have dominated the market over the past years. Our main objective is to remain at the forefront of innovation, always putting our R&D at the center whilst collaborating with external specialized companies all over the world," said Alessia Valducci, CEO.
Other players specialize by therapy. In the pure CMDO space, Genetic Spa, an Italian company founded in 2007, is looking to increase its R&D investment from 6% to 10% this year, dedicating mostly to its two therapeutic areas, ophthalmology and respiratory: "In the respiratory field, we invested in nasal sprays, nebulizers, Dry-Powder Inhalers (DPI) and Metered-Dose Inhalers (MDI). In ophthalmology, we invested in a Blow Fill Seal single-dose technology and the multi-dose technology with preservatives or preservative-free," said Rocco Pavese, the CEO.
Unlike the CRO sector, CMDOs have resisted consolidations and the market remains broadly fragmented, mostly because each technology is very different and pharmaceutical companies are used to having multiple suppliers. Nevertheless, CDMOs coming to the market with an integrated offer have a stronger competitive advantage. As part of its strategy to transition from a pure generic API manufacturer into an integrated CMDO, Icrom, an Italian CMO producing APIs and GMP intermediates, is looking to acquire a manufacturing site dedicated to clinical APIs in the US: "Over the last 10 years, we have made important investments to sustain this transition. In 2018 we opened a new R&D center and, in 2020, we completed the construction of a new and larger warehouse with QC ancillary buildings. Earlier this year, we started building a GMP clinical-scale-API manufacturing facility, which will be fully dedicated to CDMO activity," said Pierfrancesco Morosini, CEO.
Reversely, Italian manufacturing companies also present good investment opportunities to international buyers. In 2019, Lisapharma was bought from the Italian fund Arcadia by the Chinese API producer Sito Bio, a change of ownership that should help Lisapharma register its products in China. Another Italian company, Diaco Biofarmaceutici, an IV producer born in 1967, was acquired by a family of Ukrainian investors who put about 50 million euros into the plant over the past six years. Following the long period of restoration, Diaco re-entered the market in 2018, supplying IV solutions to hospitals. Besides having its own product line focused on orthopaedics, urology, gynaecology and respirator, Diaco also operates as a CMO for glass-based parenteral solutions.

Packaging and sustainability

The most recent UN report by the Intergovernmental Panel on Climate Change (IPCC) warned that the current industry and national pledges to cut emissions are nowhere near enough to start reducing the level of CO2 in the atmosphere; meanwhile, extreme weather conditions are becoming more severe and more frequent, ringing the alarm on climate change. These mounting environmental pressures raise the bar higher for the manufacturing industries.
Thankfully, the Italian pharma industry has already made important progress in reducing its environmental footprint, having almost halved both its energy consumption and greenhouse gas emissions (GHG) in the last 10 years, according to Farmindustria. The pharmaceuticals sector has invested in sustainability more than any other manufacturing industry in the country, and continues to do so.
Sustainable drug production has two broad conditions: The first is that drugs are produced with as little energy consumption and CO2 release; this has been a prime focus for manufacturers who broadly adopted green production standards. The second one is to ensure product circularity. Because the drug itself ends up being consumed, this second aspect concerns the packaging or drug recipients (such as foiled tablets, syringes, IV bags, blisters, and others).
Due to contamination risks or other hazards, drug packaging has been traditionally difficult to recycle. However, the industry is working together across the drug's life cycle. "Starting from our glass suppliers, the bottles reach hospitals, where they are passed on to waste management companies; this is

Andrea Lodetti

CEO,
BORMIOLI PHARMA

> To be an effective and competitive supplier, it is key to have a comprehensive portfolio and a strong innovation drive.

Can you introduce Bormioli Pharma and describe its core capabilities and product range?
Bormioli Pharma is a major Italian player in the global pharmaceutical supply chain, producing more than 7 billion pieces of containers, accessories, and closures that address different drug applications. These are delivered to over 100 countries. We have 10 industrial plants located in Italy, France and Germany, as well as commercial branches in the US and China. In 2020, Bormioli Pharma had a total turnover of approximately €260 million. Bormioli Pharma's expertise stretches across 10 production technologies, and we place significant importance on innovation and sustainability, partnering with our customers to develop new products and solutions. Our clients range from big pharma companies such as GSK, Merck or Roche, to CDMOs and local distributors. Over 60% of our business is international.
What has been Bormioli Pharma's role in the fight against the pandemic?
On one hand, we are producing numerous containers for therapies used to treat people with symptoms of Covid-19. On the other hand, we are supporting vaccination efforts, providing containers and closures for different vaccines including Pfizer, BioNTech, and Sputnik. We are also in close cooperation with Curevac.

Can you walk us through some of Bormioli Pharma's innovation efforts?
Bormioli Pharma's innovation efforts are structured across four main pillars. The first one is usability, through which we ensure our packages are easily handled by different people, including the elderly or people with disabilities.
The second innovation pillar is traceability. More people are buying drugs online since the pandemic. Bormioli Pharma plays a role in ensuring that the product delivered to the consumer comes from the original manufacturer. We can distinguish genuine products from counterfeits by including unique elements in the packaging.
Thirdly, we are focusing on connectivity. Internet of Things (IoT) is becoming an important part of the packaging for pharmaceutical applications. In the future, it may also allow us to track the consumer's adherence to the prescription.
Finally, and perhaps most importantly, we are focusing on sustainability. Half of our annual 7 billion pieces are made of glass and the other half of plastic. Over the past 15 years, we have been studying alternative polymers or recycling options to create circularity for our products. We are ready to offer bioplastics and compostable plastic for the dosing system, as well as different types of mechanically or chemically recycled plastics.

What is Bormioli Pharma's expansion strategy?
To be an effective and competitive supplier, it is key to have a comprehensive portfolio and a strong innovation drive. Our acquisitions follow these two objectives: First of all, we are completing our project portfolio by acquiring companies such as GCL, through which we added injectable vials to our portfolio. Secondly, our acquisitions strategy is motivated by geographical expansion. The acquisition of Remy & Geiser, a specialist in dosing systems, allowed us to strengthen our presence in German-speaking countries and northern Europe, as well as extending our offer of dosing systems. Most recently, we completed the acquisition of Iso GmbH, a specialist in vial production – a very sought-after market, especially for injectables.

What opportunities do you see in the healthcare packaging sector?
The packaging market has experienced annual growth of 4% for the last five years. Italy is the sixth-largest market for packaging in the world, and the third in Europe. As a result of the pandemic, Italy is seeing commensurate investment coming especially from the European Union, with strong recommendations for healthcare investments more generally. I expect significant cash flows coming to the country, both from domestic and foreign companies, to support production capabilities.

What are Bormioli Pharma's objectives and priorities in the next 2-3 years?
Our aim is to maintain our growth and to check M&A opportunities to improve our product portfolio, our service level to customers, and our geographical footprint. We also intend to increase investments in innovation and become a reference player for the whole pharma industry, developing innovative solutions for packaging and delivery systems. We are also advocating to our partners the importance of sustainable packaging solutions. Finally, we want to keep up with digital innovations and incorporate digitalization in our packaging solutions wherever possible. ■

We are committed to reducing our environmental impact, but we must also make sure we secure adequate shelf life; a balancing act which requires a lot of innovation. Our goal moving forward is to find the right balance between safety, protection and sustainability in designing the best packaging solutions in the market.

- Valentina Bianchini, Marketing Director, Encaplast

where the waste company intervenes to sell the glass back again to our glass providers," said Alan Zettin, the CEO of Diaco Biofarmaceutici, an IV producer.

Diaco sources its glass from Bormioli Pharma, one of the largest packaging companies. Bormioli produces containers, accessories and closures used in different drug applications in 100 countries and to reputed customers like GSK, Merck, Roche, as well as to CDMOs. Out of its seven billion pieces produced, half are made of glass, and the other half are of plastic. Some of its customers, like Diaco, choose only glass, attentive to the introduction of plastic taxes. In January this year, the EU introduced new national contributions based on non-recycled plastics as a source of revenue for the EU budget.

Image courtesy of Cambrex.

Catering to these regulatory changes as well as demand trends, Bormioli offers alternative polymers or recyclable plastics. "Sustainable solutions are becoming increasingly more demanded by the pharma industry, many players have declared their goals to become carbon neutral in the next decade. We are ready to offer bioplastics and compostable plastic for the dosing system, as well as different types of mechanically or chemically recycled plast,ics," said Bormioli's CEO, Andrea Lodetti.

Other materials come with different sustainability profiles. Carcano, another large packaging company with over 150 years of history in the market, offers aluminium solutions, in the form of aluminium foil used to create blisters and cold forming. Aluminium is generally considered a very environmentally friendly and easily recyclable metal; in fact, recycling the material saves 95% of the energy used to produce it from scratch. Italy has a functional recycling ecosystem in place, handled by different associations under the umbrella of CONAI consortium (Consorzio Nazionale Imballaggi), which operates a system of recovery and vaporization of different materials, including aluminium, paper, plastic and glass. Carcano is part of the aluminium association: "We are very active in promoting the collection and recycling of aluminium and we are the first Italian company that has successfully achieved the ASI Performance Full Standard certification for our 3 facilities," said Alberto de Matthaeis, general manager at Carcano.

Finally, replacing plastic-based pharmaceutical packaging with alternative, more sustainable materials can be particularly challenging if the new materials do not have the same protective properties. For instance, bioplastics may not secure the same shelf life or compliance standards as usual plastics. Encaplast, a smaller packaging company with about 100 employees, offers post-consumer materials and 100% recyclable materials after years of R&D to find the perfect combinations: "We are bringing to the market eco-packaging solutions made of biodegradable materials using cellulose as a raw source, for instance. Also, we have a range of materials suitable for E-BEAM serialization, which is eco-compatible because it does not release any chemical residues, being safe for both the environment and for human health," said Mario Neri, CEO of Encaplast.

The challenges around offering both protection and a sustainable solution have opened the door for innovative, new players. Nanomnia is an Italian start-up that offers fully organic, bio-degradable, microplastic-free encapsulation services for the pharma, agrochemicals, nutraceuticals, cosmetics, and smart material compounds industries. Marta Bonaconsa, the CEO and co-founder of Nanomnia, explained the principles of encapsulation, a process inspired by how living cells captivate their compounds in capsules: "We copied this mechanism and exploited how cells and organisms communicate between and among themselves. For pharma, we can formulate tailor-made encapsulation solutions for selected delivery of the active compound in a target biological tissue. This technology allows us to plan a lower dosage and therefore a reduced risk of side effects, but also higher stability because we expand the time-window that the active principle exerts its effect by." ■

Alberto de Matthaeis

General Manager,
CARCANO

> Our electricity needs are covered by renewable sources, of which 15% by our own hydroelectric power plant.

Can you introduce Carcano?
Carcano has been dedicated to aluminum production for almost 150 years. The company has three production units: our historical production plant in Mandello del Lario, a rolling production unit in Delebio, and a brand-new converting unit in Andalo Valtellino. While the Delebio plant is focused on primary aluminum processing, the other two are focused on converting processes for packaging and industrial applications. We are spread out throughout northern Italy, between Lecco and Sondrio. Our yearly turnover is approximately €180 million, with an annual output of about 42,000 tons.

Can you provide an overview of Carcano's product offering and main capabilities?
For the pharma industry, we offer three types of products. The aluminum foil from our own factory is sold to converters for the pharma industry, but mainly is used to produce two types of semi-finished products: blisters or cold forming. Blisters can be produced in combination with PVC or with aluminum. When they are produced with aluminum, this is called cold forming, which is a more complex product that also includes two other plastic inserts.
Carcano offers volume, reliability, and quality performance. Our differentiating strength is that we can handle additional volumes or have backups in case of an unexpected event in one production unit thanks to our reliance on two factories. This is a much appreciated quality by the pharma industry which needs to have safe supplies and reliable partners. Our R&D team is constantly developing new ways to improve our products. For the pharma industry, we have developed new lacquers to achieve better performances.

What is the sustainability profile of aluminum and what opportunities for recycling are in place?
In Italy, several associations deal with the recycling of different raw materials. These associations are under the umbrella of CONAI consortium (Consorzio Nazionale Imballaggi) that operates a system for the recovery, recycling and valorization of steel, paper, plastic, aluminum or glass. We are part of the aluminum association. Carcano is very active in promoting the collection and recycling of aluminum, whose unique properties make it a preferred material, protecting products from air, water and light. Carcano is the first Italian manufacturing company that has successfully achieved ASI Performance full Standard certification for its 3 facilities.
The ASI Certification program was developed through an extensive multi-stakeholder consultation process and is the only comprehensive voluntary sustainability standard initiative for the aluminum value chain.
Carcano has also been certified by ISO 50001 since December 2017, which means that our energy consumption is continuously monitored. In 2018, we prepared a 3-year performance improvement roadmap, which has allowed for significant energy savings throughout these years. Our electricity needs are covered by renewable sources, of which 15% by our own hydroelectric power plant. We have also introduced LED lighting and established hydraulic units and insulations to reduce energy consumption.

Which are the company's most important markets and how do you plan to increase your international footprint?
The Italian market accounts for 40% of our total revenues. We would like to consolidate our presence in the US, which is a big market of great potential. As a vertically integrated company, we are quite unique in the aluminum transformation and converting space. This quality allows us to stand out and ensure supply continuity and a trustworthy end-to-end service to partners.

What is Academia 13 and how does it reflect Carcano's values?
Academia 13 is a tailor-made professional academy, which was established to transfer know-how within the company. The academy allows both blue-collar and white-collar professionals to learn from each other and share their expertise. The key mission of Academia 13 is to bring together people from different production units, different functions and top management as well. We seek to promote open discussion about practical matters. 2020 was very disruptive for the academy, in-person meetings becoming impossible to carry out; however, we will restart this activity in September 2021.

What are Carcano's key objectives in the next 2-3 years?
Simply put, our goal is to grow, and we are on track to achieve this. Our new plant in Andalo will soon be used at full capacity, maximizing total efficiency, while the other two plants continue to run in a stable way. With these multiple production processes in motion we can meet both long-run and short-run production targets, as well as dedicating production lines to specialty products, and the other to standardized products increasing the overall efficiency. Our optimized production schedules and processes will drive organic growth over the next few years. ■

Out-of-pocket opportunities

Growth has been lacking in Italy's non-prescription drugs sector for over a decade. "From 2010 to 2020 the average annual contraction of consumption was -3.3%," affirmed Salvatore Butti, president at Assosalute, the association that represents non-prescription medicinal products authorized to be advertised to the public.

The pandemic, unfortunately, did not help. The outbreak brought radical changes to our life habits. Social distancing as well as the use of masks and hand sanitizer significantly reduced the circulation of the influenza and parainfluenza viruses. This resulted in a strong contraction in cough and cold OTC medicines sales.

While products such as cough and cold medicines experienced a massive drop in 2020, Italy experienced astoundingly high levels of growth in the sales of herbal supplements, vitamins, and minerals. Indeed, the idea that vitamins and food supplements could help against Covid-19 by strengthening people's immune system became prevalent across Italian newspapers, encouraging people to focus even more on prevention and wellbeing. Probiotics became the most consumed dietary supplements in 2020, followed by vitamins and minerals. Today, eight out of 10 Italians consume vitamins and dietary supplements regularly.

As a response to the increased demand of immunology boosters, several companies adapted their product offering and came up with new product lines. The San Marino-based producer of food supplements Erbozeta introduced the Luxfluires line, a set of products aimed at increasing the natural defense of the immune system. Vittorio Broccoli and Maud Saillard, export sales executives, also noted a rise in demand for products used in sleeping disorders and anxiety as a consequence of the pandemic and strict lockdowns. "Our Melacron line includes sprays for fast absorption and therefore a quick benefit, but also slow-release tablets that ensure a good night's sleep throughout the night," they explained.

The pandemic also boosted an existing trend, as Italian domestic players have a big heritage in naturally derived products. The consumption of herbal supplements, vitamins and minerals grew at a rate of 5.6% in the period 2014-2018*. Traditionally, Italy has been a key geography of the nutraceutical market, thanks to the widespread awareness of the importance of a balanced diet and a healthy lifestyle. In a context of an ageing population, Italians have also been becoming increasingly focused on disease prevention and supporting living practices to increase a healthy life span. Mastelli reflects the Italian tradition of naturally derived products; it is a 70-year-old Italian company specialized on two natural molecules with interesting regenerative features: Polynucleotide (PN) and Polydeoxyribonucleotide (PDRN). Their entire product portfolio is based on these natural substances, including injectable solutions for aesthetic medicines, orthopedics for intrarticular tissue, or products for dermatology and gynecology. "Our legacy product is Placentex, a topical cicatrizant and anti-dystrophic drug with over 50 years of history," underlined Fabio Fiscaletti, CEO.

Innovation

While the level of innovation of non-prescription medicines is lower than other lines of the pharma business, the sector constantly invests to optimize their dosages and routes of administration, increasing their effectiveness and reduce any contraindications and interactions. PharmaNutra Group, for instance, is a leading player in iron-based oral nutritional supplements and is enjoying great success thanks to its Sucrosomial technology; a unique patented delivery system developed to reduce the side effects associated with iron intake and to facilitate the absorption of this mineral. "Our technological pillar is iron, and the Sucrosomial iron technology is found under the Sideral brand, of which we derive 16 formulations adapted to different regulations in 54 countries. However, we apply this technology to other minerals like magnesium, and our UltraMag nutritional supplement is already sold in six countries," expressed founder and president Andrea Lacorte.

Similarly, Valpharma, a company present both in pharmaceutical and nutraceutical-phytotherapeutic areas, invests constantly in technological innovation. "The latest nutraceutical products of our group have built upon the knowledge developed by our technicians in the pharmaceutical field, particularly in the area of modified release, providing added value to customers," highlighted Alessia Valducci, CEO.

However, innovation in non-prescription medicines goes beyond product development, as in many cases, companies look for ways to build new relationships between patients and health providers and to improve their strategic marketing. Montefarmaco OTC, a small but specialized player in the consumer healthcare sector, covers the main segments of the self-medication market including probiotics, ophthalmic, laxatives, painkillers and skin products. From product development to commercialization, the company innovates in line with market needs and cultural dynamics. "One of our best examples of beyond-the-product innovation is our M-Cap System packaging, a design 100% made and patented in Italy, 100% recyclable and user-friendly," said Stefano Colombo, general manager. ■

* https://www.pwc.comit/it/publications/assets/docs/Vitamins-Dietary-Supplements-Market-Overview.pdf

Salvatore Butti

President,
ASSOSALUTE - FEDERCHIMICA

The self-medication sector could be of help in defining a new governance of the healthcare system through the definition of new models of collaboration between GPs and pharmacists as the first reference points for minor ailments.

Could you introduce Assosalute to our audience?
Assosalute is the Association within the Italian Federation of Chemical Industry (Federchimica) that represents non-prescription medicinal products authorized to be advertized to the public.

How important is the non-prescription market to the broader Italian life sciences ecosystem?
The non-prescription medicines sector accounts for 14.5% of the retail pharmaceutical market in Italy. The level of innovation of non-prescription medicines is, by definition, lower compared to other pharmaceutical products, and it is exclusively linked to updates and replacements (switches) of already existing medicines.
However, OTC companies invest consistently in order to innovate and renew existing products, looking at innovation areas such as the optimization of dosage forms or routes of administration, with the goal of improving product effectiveness and reducing the risk of contraindications or undesired effects.
The sector offers therapeutic solutions for the treatment of minor ailments, thus supporting individuals' health and, potentially, the health care system. Increasing the offer of non-prescription active ingredients that are currently unavailable in Italy would allow savings on public pharmaceutical expenditure and a reallocation of resources in favor of the research and modernization of the Italian National Health System.

Could you give us an overview of the main regulations in the OTC and other non-prescription medicines?
The Italian regulation of non-prescription medicinal products follows the European regulatory framework. The Italian Ministry of Health must approve advertising in advance, while the switch criteria are the same as established in the European Medicine Agency Guidelines on the classification of OTC medicines.

How has the sector performed during the pandemic?
In 2020 the sector registered negative growth: The sector saw a contraction of 8.8%, with a turnover reduction of 6.6% - the equivalent of €2.3 million. In total 235 million boxes were sold. The use of masks, social distancing, greater hands hygiene, and the overall contagion containment measures have significantly reduced the circulation of influenzas and parainfluenza viruses. Cough and cold OTC represent the biggest therapy by market share in the OTC sector, and, consequently, there has been an acerb contraction in this segment, driving down the sector's overall performance.
At the same time, the pandemic brought more awareness about health and prevention, also shifting more emphasis to the importance of general wellbeing. Because of these trends, the food supplements sector enjoys a positive sales curve, continuing a trend started over the last decade. The high growth in nutraceuticals and food supplements has eroded the market share of non-prescription medicines used in minor ailments, also because these are subject to stricter regulations in terms of marketing and advertising.

What are the main growth areas in the Italian non-prescription drugs sector? What are your projections for the industry going ahead?
The 2020 sales decline risks to damage a sector already hampered by stagnant growth in the last decade; from 2010 to 2020, the average annual contraction of consumption was of -3.3%. To reverse this trend the sector needs recognition for its contribution in supporting the challenges of the National Health System. In this context, the expansion of the self-medication sector can make room for economic resources to be deployed where they are most needed. The self-medication sector could also help define new governance structures for the healthcare system, by improving collaborative models between GPs and pharmacists as first points of reference for minor ailments.

What are Assosalute's objectives for 2021-2022?
In 2021 Assosalute will launch a national project for a new model of collaboration between medical doctors and pharmacists. We are looking to make a case for the importance of OTCs for citizens' health, as well as the sector's contribution to the national health system and its long-term viability, highlighting how pharmacists and doctors can play a role in redefining this sector. ■

Andrea Lacorte

Founder and President,
PHARMANUTRA GROUP

> Over the past 20 years we have grown into a leading player in the iron-based oral nutritional supplements market.

Could you introduce PharmaNutra Group and give us an overview of its three companies?
The Group was founded almost 20 years ago in Pisa (Italy), and it is formed of PharmaNutra S.p.A., Junia Pharma S.r.l., and Alesco S.r.l. Alesco was the first entity of the Group to be established and it is focused on the production and distribution of ingredients and raw materials in the B2B market. Meanwhile, PharmaNutra is concerned with FDFs (nutritional supplements and medical devices) using the innovative materials produced by Alesco. Finally, Junia Pharma is dedicated to the needs of the paediatric sector.
Over the past 20 years we have grown into a leading player in the iron-based oral nutritional supplements market. Our biggest strength is that we operate in a protected environment: We use patented Sucrosomial ingredients, controlling our brands globally. Our technology is medically proven, backed by over 120 published scientific studies.

Could you walk us through your current portfolio?
Our technological pillar is iron, and the Sucrosomial iron technology is found under the Sideral brand, of which we derive 16 formulations adapted to different regulations in 54 countries. However, we apply this technology to other minerals like magnesium, and our UltraMag nutritional supplement is already sold in six countries. Besides, our cetylated fatty acids technology is the key ingredient for our Cetilar brand medical devices line, with cream, patches and tape topical applications customized to different users.

A third of PharmaNutra's revenues is export-based. How do you position for international growth?
We actually export 65% of our output by unit volume. This discrepancy comes from the fact that we use distributors abroad, and these extra costs reduce the gross margins. Our strategy down the line is to maintain the distributor model in smaller markets, but change the approach towards key large markets by establishing subsidiaries through acquisitions. US, Canada, UK, France, China, Japan and Australia are the most important markets where we see ourselves growing in the future.

PharmaNutra Group was recently qualified to the STAR segment of the Borsa Italiana (Italian Stock Exchange). Can you comment on this milestone and how is it impacting your investor base?
After listing on the AIM three years ago, last December we entered the STAR segment of the MTA. This upgrade creates significant changes, both internally and externally. At an organizational level, we need to communicate more frequently and more accurately, reporting a quarterly balance sheet. The profile and nature of our investors have also changed significantly; this means more demanding investors, who are interested in the fundamentals of the business. Also, the investor base is more geographically diverse, with many brokers in Southern and Northern Europe, as well as in the Americas. Just by entering the STAR segment, the appreciation of our stocks improved greatly, and we duplicated the value of the company in less than six months.

What is your inorganic growth strategy?
PharmaNutra's key priority in this period is to expand through acquisitions, both domestically and internationally, with two main goals: In Italy, we are going to strengthen our team of 140 sales agents and diversify our portfolio by adding specialist products like self-prescription medicines or sports supplements. Abroad, we are actively scouting for companies that fit our portfolio. Essentially, we look for companies with a reliable scientific reputation and a smart approach to medical promotion and distribution that could support the spread of our technology and products through their channels.

What are your investment priorities?
Because we are growing so quickly, we are building a new, more equipped and avant-guarde HQ in Italy. Also, we are investing in a production plant dedicated to the biosynthesis of our Sucrosomial technology, from where products will be sent to separate facilities for the end products. Finally, we are building Europe's largest cell biology cruelty-free lab that allows us to simulate the digestion and absorption of compounds without involving animal testing. We should inaugurate the new office, the plant, and the new digestion lab in the next two years.

Do you have a final message for our international audience?
The potential of PharmaNutra is gigantic. If we look at our performance in our top 10 markets, it is not a dream to think we can multiply the success in big markets like the US. ■

Stefano Colombo

General Manager,
MONTEFARMACO OTC

> Montefarmaco's portfolio covers the main segments of the self-medication market, including probiotics, ophthalmics, laxatives, painkillers and skin products.

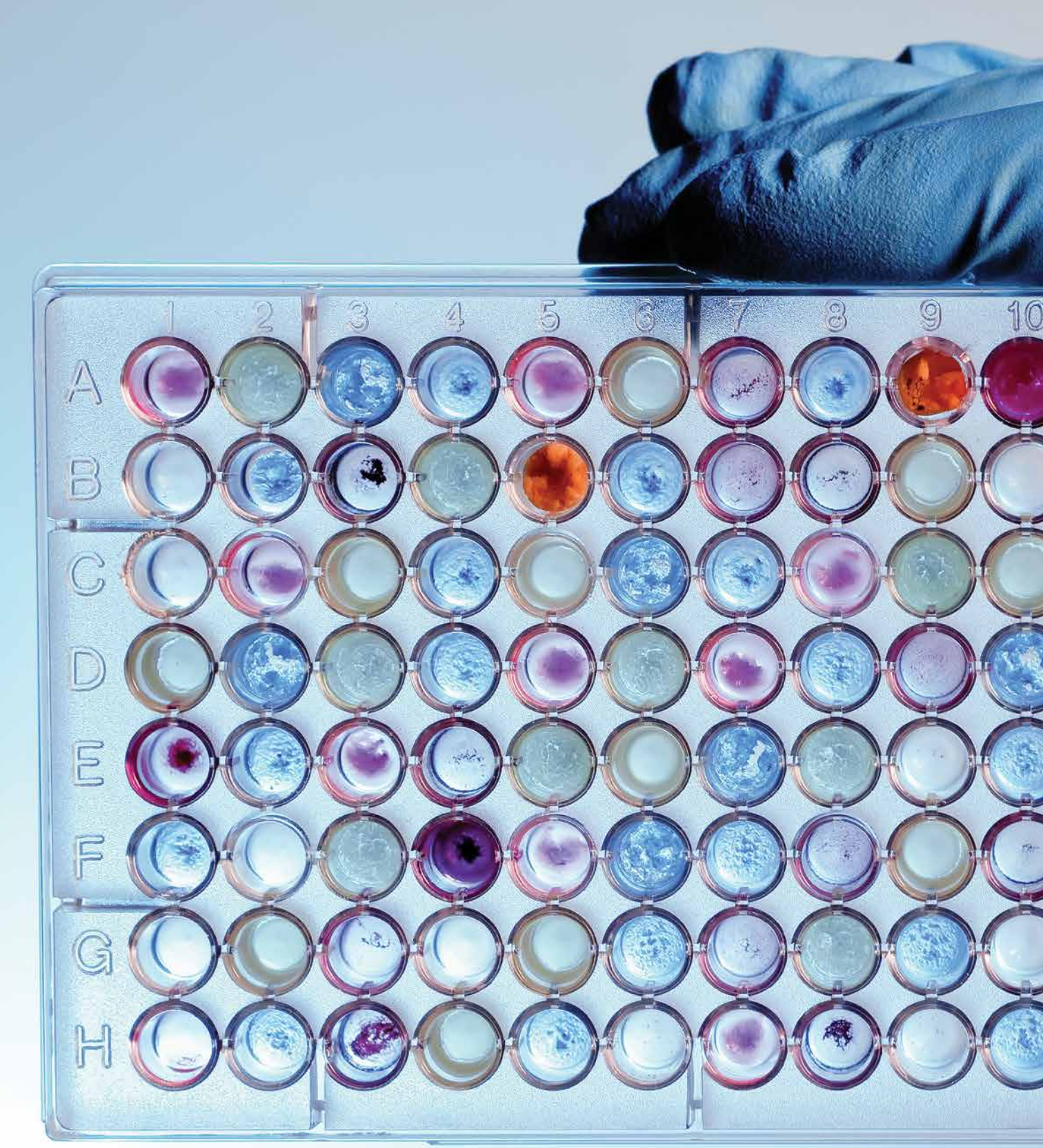
Montefarmaco is one of the first OTC players in Italy. Can you tell more about its evolution?
Montefarmaco OTC was founded in 1945 by my grandfather, Giovanni Colombo, and today we are proud to be a business led by the third generation of pharmacists. Back in the 1970s when the OTC segment came to prominence, we were amongst the first to convert our prescription portfolio into a non-prescription one, selling directly into pharmacies. At that time, my father had a very inspired vision that pharmacies would be playing a more important role in wellbeing, which turned out to be true. The new millennium was characterized by both organic and inorganic growth. By 2012, we started outsourcing our production. We believed this was a fundamental decision to make. Marketing and R&D are the mainstay of Montefarmaco, so we decided to focus on innovation. Today, we are supplying directly to 12,000 customers.

Could you share more details about your current portfolio and the main innovation areas?
We are a small but specialized player in the consumer healthcare segment, including drugs, food supplements and medical devices. Our products enjoy leading market positions, and we showcase blockbuster drugs like Lactoflorene or Iridina. Montefarmaco's portfolio covers the main segments of the self-medication market, including probiotics, ophthalmics, laxatives, painkillers and skin products. Given our legacy as a pioneer in the probiotics market, this remains our main focus, followed by eye drops, vitamins and minerals. From product development to commercialization, the company innovates in line with market needs and cultural dynamics. One of our best examples of beyond-the-product innovation is our MCap System packaging, a design 100% made and patented in Italy, 100% recyclable and user-friendly. This obtained the Oscar dell'Imballaggio "Best Packaging" award in 2020. I believe our innovation approach relies on our ability to stay curious and discover what is not yet on the market.

Last year, Montefarmaco acquired Swiss-based distributor of Polaroid hearing aids, Jordan Tech. What motivated this acquisition and what opportunities do you see in the OTC hearing aids market?
We had been working with Jordan Tech for two years prior to the acquisition, becoming well acquainted with this market. Hearing loss is becoming more common as populations age, and this is a condition that disconnects the person from the surrounding world. Seriously impaired patients will clearly see a specialist, but there is a booming segment represented by people with mild hearing impairment who can simply walk into the pharmacy to buy hearing aids to amplify the sound around them. The Polaroid trademarked hearing aids offer a very good quality-price balance, and we are working with pharmacies to market these aids directly, creating a win-win-win situation for all parties: patients can enjoy a better quality of life, pharmacies have a means to draw people into the shop and to be close to an emerging consumer need, and we are tapping into a market of very promising potential.

What is Montefarmaco's international footprint and what are your focus markets?
Our internationalization took off more seriously since 2007, with a small subsidiary in Romania. Our focus has been on Europe, Russia and China, where we are present with trading subsidiaries. In Russia, we are already distributing through a local player and we are in search of additional partners. In China, we began our cross-border business in 2019 with a few product registrations. As populations age, there is a rise in chronic diseases and more attention is paid to prevention. Also, the purchasing power in these key countries is growing, which makes room for more sophisticated products, especially for those products with a "Made in Italy" label. Besides these two markets, we continue our scouting activity for potential partners in the Middle East and other European countries. Before the pandemic, we were also exploring the possibility of US expansion, but moving restrictions have put these plans on hold for now.

Could you summarize your future ambitions for the company?
As a next priority, we'd like also do incorporate medical detailing into our business model. In order to do so, we are considering to purchase companies already active in medical detailing, in order to cover both promotional drivers: the pharmacist and the doctor. We have a new cosmetics product range called Ontherapy, with application for skin side effects as a result of oncological treatment. Finally, we aim to continue our international expansion and reach a target of 25% of our revenues coming from export markets.■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INNOVATION

"Funding for early-stage development remains generally limited, and Italy lags behind countries like France, which sees more liquidity. Pricing and market access are challenging in Europe, and more so in Italy, and this aspect hinders the valuations needed for early-stage programs, even though we have seen some legislative developments to award funds to innovative orphan or oncology drugs."

- Fabrizio Chines,
Chairman & CEO,
SIFI Group

Drug development and discovery

THE TECH TRANSFER VALUE CHAIN

Around the same time as Moderna started working on its messenger-RNA Covid vaccine, Italian company Takis Biotech started developing the first DNA-based Covid vaccine in Europe. But, while the American biotech was already preparing GMP batches just 42 days after the Chinese published the sequence of the virus, Takis lacked the infrastructure to move that fast. Today, Takis' Covid-eVax is moving to Phase 2 clinical trials. Meanwhile, the only other Italian company developing a vaccine against the SARS-CoV-2, ReiThera reported encouraging results in Phase 1 and Phase 2 clinical trials, but it is unclear how it will fund later-stage trials requiring thousands of volunteers. A court of audit overseeing public spending ruled against a 50 million euros government investment into the company.

Italy has a large pool of talented, passionate and hardworking people. However, over the last 30 years, the country has lost all its MNCs, not only in the pharmaceutical industry but in most of the industrial sectors. To fuel a model of global culture, Italy has a long way to go.

- Riccardo Carbucicchio, CEO, NTC

In the race to develop a Covid vaccine, the full value chain of innovation, including investors, regulators and governments, has been put to the test together with the scientists, and it is no surprise to see that the few vaccines available today were created in the world's most powerful countries for innovation. The story of Italian biotech is one of scientific excellence insufficiently valorized due to a lack of industrial and financial catalysts.

On the one side, Italy has a great academic inheritance in biotech and medical science, is the sixth in the world for the number of clinical papers published, and a pioneer in the use of stem cells and genetic therapy, according to Anna Formosa, country manager of CRO Pharm-Olam. On the other side, the established pharmaceutical industry is more focused on manufacturing and commercial activities. This leaves both scientists and start-ups without an industry receptor.

Ideas and innovation, however, abound. There are 344 healthcare biotech Italian enterprises in Italy, but these only represent a total revenue of 9 billion euros in value, according to Assobiotec, the Industry Trade Association for the Development of Biotech in Italy. Moreover, 90% of these are SMEs. "The sector is particularly dynamic and truly motivated to innovate and grow, but we pay the price for huge juridical, fiscal and regulatory obstacles. The result is the very small average size of the Italian biotech enterprises, with many valuable ideas and projects struggling to reach the stabilization phase," said Ricardo Palmisano, the president of Assobiotec. Franco Lori, the CEO of Italian drug discovery company Virostatics, calls this disconnect between the different actors "the Achilles" hill of Italian drug development: "The Italian pharma industry counts a few great names, but we are missing the culture of bringing a drug from pre-clinical to leading the market. This is why we need to seek out partners in the UK, Switzerland or the US, rather than Italy."

Fabio Bianco, the CSO of early-stage life sciences incubator Bio4Dreams, boils it down to a lack of tech transfer culture. The "tech transfer office" is typically realized at the univer-

Riccardo Palmisano

President,
ASSOBIOTEC

> The sector is particularly dynamic and truly motivated to innovate and grow, but we pay the price for huge juridical, fiscal and regulatory obstacles. The result is the very small average size of the Italian biotech enterprises, 90% of these being SMEs.

Could you briefly introduce Federchimica Assobiotec?
Assobiotec is the Industry Trade Association for the development of biotechnology in Italy. It represents approximately 120 companies, as well as science and technology parks operating in healthcare and bioeconomy, including agriculture, industry and environment.

Could you highlight some recent developments for the association?
Biotechnology is ever more important in different fields of application. During the pandemic, biotech provided answers and solutions in all the phases of the crisis management, from sequencing the virus genome to molecular diagnostic tests, vaccines, and monoclonal antibodies. Assobiotec carries out ambitious projects to push industrial policy in favor of biotechnology innovation, and our role has been constantly evolving. Due to the heterogeneous nature of our associated companies, we focus on many areas of innovation and advocacy, such as orphan drugs, advanced therapies, diagnostics, clinical trials, access to innovation, manufacturing, fiscal rules, incentives to innovate, new breeding techniques, circular economy and others.

The health biotech industry is a growing one in Italy. What characterizes this sector?
Italy has an excellent academic and research tradition, with a labor cost lower than many other European countries. The sector is particularly dynamic and truly motivated to innovate and grow, but we pay the price for huge juridical, fiscal and regulatory obstacles. The result is the very small average size of the Italian biotech enterprises, 90% of these being SMEs. The post pandemic PNRR and the Next Generation EU funds could be an unrepeatable opportunity to remove obstacles and to exploit the potential of the Italian biotech sector.
The BioINItaly Report 2020 – realized by Federchimica Assobiotec with ENEA – counts 344 enterprises in the health sector (49% of the total number of biotech enterprises in Italy) with over 9 billion euros revenues value (75% of the total revenues value). The health sectors also collects the majority (91%) of R&D investments and the highest employment rate (75%) for Italian biotech R&D.
The startup ecosystem is extremely fertile: between 2017 and 2019 more than 50 new innovative startups have been recorded in biotechnologies. Unfortunately, many valuable ideas and projects often struggle to reach the stabilization phase.

What are the key therapies that biopharma companies look at? How has the pandemic influenced their focus/ operations?
Italian biotech massively invests in unmet medical needs including therapeutic solutions for oncology, infectious diseases and neurology. A special mention is also deserved for diagnostics.
The contribution of national biotechnologies in the collective mobilization for the fight against the SARSCoV-2 has seen and is still seeing an important role into gene sequencing of the virus, identification of the receptor responsible for the disease, diagnostics, but also in the development of vaccines, antiviral drugs, and monoclonal antibodies. Italian biotech companies are also at the forefront of this global battle.

How do you see investment appetite in biopharma?
At the end of 2019, 25 financing transactions for a total of approximately 152 million euros were recorded in Italy. The record places our country as recipient of 5% of European investments and 1% of global investments. The average cut for investment in biotech, which stands at around 6 million euros, is underpowered compared to the European average (20 million euros) and despite some significant placements, national numbers remain too low.
However, the government has recently made different regulatory interventions in the right direction, such as eliminating tax for 3-year exits in innovative startups; for companies carrying out R&D activity for innovative drugs, there is a tax credit of 20% for costs incurred between 1 June 2021 to 31 December 2030; this is extended to foreign companies carrying out R&D activity in Italy, increasing the cap from 4 to 20 million euros per year for each beneficiary.
Furthermore, the Enea Biomed Tech Foundation is now re-shaped with a strong focus on biotechnology and innovation.
These are all actions that we believe can give concrete help to the development of our startups and SMEs. ■

sity level in countries like the US or the UK, but without this filter, ideas reach investors or industrial partners too early. There are two issues related to this. First, a poorly structured project will not earn the trust of investors. Second, investors may not understand the complexities of new drugs, together with clinical, regulatory, or pharmaco-economic aspects. To Bianco, the cultural change that needs to take place is to convince the industry and start-ups alike to start by engaging on a scientific level first, rather than going straight into commercial matters, which is what currently happens. Bio4Dreams works with start-ups in advanced therapeutics, diagnostics, medical devices, AI, as well as blue and green tech, in a bid to shape and de-risk a project before it is ready for the next step of development – be it financing or a partnership.

The current appetite for high-risk ventures comes from the fact that there is high liquidity in the market, so investors do not mind taking risky bets. However, this environment will soon change and investors will search for safe havens and companies that can generate long-term revenues with lower risks,

- Alessandro Della Chà, CEO, Cosmo Pharmaceuticals

Funding

The next big issue is funding. According to the latest figures from Assobiotec, 25 financing transactions worth 152 million euros were carried out in 2019, which makes Italy the recipient of 5% of European funds and 1% of global investments. For the average biotech investment, Italy receives 6 million euros, compared to a European average of 20 million euros. While it may be easier for big pharma companies to attract investment, Italy's biotech sector is very early stage – out of the 375 new therapeutic projects under development in Italy, only 73 are in clinical phase. This is the stage when funding is both most critical and most difficult to pin down.

Without many options, biotech encapsulation start-up Nanomnia managed to raise 400,000 euros through crowdfunding. Its founder, Marta Bonaconsa, considers raising capital in Italy is very challenging: "It is especially difficult for biotech companies who don't have the same scalability potential as digital start-ups relying on replicating an already existing business model. Venture capitals are almost non-existent, while crowdfunding and crowdsourcing platforms are gaining popularity but are not very strong yet."

The Italian VC scene is small, about 10 times smaller than France's, according to some sources, but a few Italian firms have become more prominent in recent years. Fabrizio Chines works as an advisor for Panakès Partners, one of the first Italian funds fully dedicated to life sciences. This year, Panakès raised 150 million euros and it hopes to reach 180 million euros by the end of 2021. Having recently expanded its focus from med-tech to biotech, the VC already received 500 requests from potential targets. "Funding for early-stage development remains generally limited, while pricing and market access challenges hinder the valuations needed for early-stage programs," said Chines.

Some international VCs have also made their way to Italy. French venture capital firm Sofinnova Partners, which specializes in healthcare and sustainability, invested in Enthera Pharmaceuticals, an Italian start-up dedicated to the development of first-in-class biologics for the treatment of Type 1 Diabetes (T1D) and Inflammatory Bowel Disease (IBD). Enthera is also backed up by some corporate investors, including Roche Venture Fund and AbbVie Ventures, which helped the company to raise 35 million euros in a Series A financing – a record for the Italian biotech industry. The money will fund two clinical trials, but Enthera will need at least 80 million euros to bring the novel therapeutics into the market. The lead clinical candidate is already in GMP production, and the first clinical trial with healthy subjects is scheduled for the beginning of 2022.

Enthera's success is an encouraging sign for biotech, including higher-risk, higher-value biotech therapies without equivalent on the market. "Existing therapeutic options for the degenerative diseases we target can only slow down or stop progression, but there is currently no real-disease modifying treatment that can revert the destruction of the organ," said Giovanni Amabile, the CEO of Enthera.

The great attention paid to biotech since the beginning of the pandemic has certainly ignited investor appetite in the sector, both healthcare and non-healthcare investors picking up on life sciences. Data from McKinsey indicated that the average share price of European and US biotechs increased at more than twice the rate of the S&P500 between January 2020 and January 2021, biotech over performing its related industry, pharmaceuticals. Meanwhile, VC activity grew by 45% in a year, based on the same source. BCIG reported that VCs invested 60% more by January 2021 than they had in the previous year.

This offers a good opportunity for both established start-ups waiting on their big break, but also for new start-ups, born as a result of the new needs that the pandemic created. For instance, Biomedical Pharma is a fresh start-up spinning off from Power Metal in 2020. In collaboration with the University of Siena, it came up with a non-toxic, photocatalytic sanitizer containing a colloidal resistant material on different types of surfaces. The patent is known as PhotoACTIVE Technology and is already the mark of five products. Its founder and CEO, Omar Alessandrini, believes the increased focus on hygiene is here to last: "The pandemic has brought a change in peo-

ple's mentalities and habits, and the need for products that eliminate viruses and bacteria from surfaces and fabrics will surely persist; in fact, it is estimated that €28 million will be dedicated to research on antiviral and antibacterial products in the textile industry over the next few years."

However, some Italian industry leaders are cautious about an expected investment boom in biotech or innovation more broadly. Franco Lori, the CEO of Virostatics, expects a short-lived hype, a mere reaction to the emergency that will eventually fade: "One would be tempted to argue that the pandemic created more willingness to invest in addressing health challenges; there is also a large cash opportunity in Italy, and we have a prime minister well familiarized with the EU mechanisms. But besides these pluses, we have a cultural minus: we are not used to thinking about long-term investments. Cultural change is the slowest to occur, which is why I don't expect a dramatic change driven by the pandemic," he said.

Observing long-term market tendencies, Alessandro Della Chà, the CEO of Cosmo Pharmaceuticals (SWX: COPN), also noted a trend whereby the value of a company goes up with the release of clinical results before it drops down again once final results are confirmed. This indicates volatile sentiment in some investor groups. "During the pandemic, numerous companies took an opportunistic approach, coming up with Covid-19 programs. Given the advancement of vaccinations, investing in Covid-19 related treatments should be taken with caution," Della Chà said.

The pandemic has brought tremendous opportunities to the life sciences, first of all by bringing down walls, be they geographical or domain-based. It has become very common to create transversal teams with chemical scientists working side by side with computer scientists, but also to look for human expertise across borders.

- Fabio Bianco, CSO, Bio4Dreams

The globalization of research

Never before at such a scale, nor more united across a common goal, have scientists around the world worked together to bring a vaccine to the market at record speed. With every successful vaccine story built on a collaboration – Pfizer and BioNTech, AstraZeneca and Oxford University, or in Italy, Takis Biotech and Rottapharm Biotech – open innovation is getting closer to becoming the status quo of biotech research. Fostering an open innovation climate is Italy's best chance in driving its ideas, be them in pharma, biotech, or med-tech, into the market.

In Europe, about 20% of all research takes place outside corporate boundaries, through the interim of universities, SMEs, start-ups, clinical centers, or CROs, according to Farmindustria. In Italy, a few high-profile collaborations in the biotech space come to mind, such as Dompè's partnership with the Universities of Chieti and L'Aquila in the development of the first ever biotech therapy to treat neurotrophic keratitis, a rare disease affecting the eye cornea, and which can lead to blindness. Italy has also developed prolific hubs in support of open innovation, such as the San Raffaele Biomedical Science Park, one of the largest in Europe, or, soon to be opened MIND (Milan Innovation District), a multi-disciplinary smart-city waiting to receive about 60,000 researchers in the next eight years.

One of the most successful Italian open innovation stories is Holostem Terapie Avanzate, a spin-off from the University of Modena and Reggio Emilia that partnered with large Italian player Chiesi. Holostem was founded in 2008 and is the first biotech company fully devoted to advanced therapies medicinal products (ATMPs) based on epithelial stem cells. The successful, three-way collaboration led to the development and registration of Holoclar, the very first regenerative medicine product used in stem cell deficiency (LSCD). Holoclar received market authorization in 2015, becoming the first such drug available on the market. In 2020, Holostem recalled the marketing rights of Holoclar from Chiesi in order to assume a more complete service, which involves direct contact with clinical centres and physicians.

In the med-tech space, Newronika was also born as a university spin-off, this time from the University of Milan in collaboration with the Hospital Maggiore in Milan. Newronika came up with an implantable brain system that can read brain activity in order to correctly adjust neurostimulation. The process is a therapeutic procedure known as Deep Brain Stimulation (DBS) used to treat movement disorders such as Parkinson's Disease. Newronika's innovation to the approach is an adaptation of the closed-loop pacemaker applied to DBS. "We developed the decoding of the brain signals to understand whether a patient is responding well or if we need to adjust the stimulation. We record the signals after the implantation of the electrode after just a few days, and only then do we implant the IPG (implantable pulse generator)," said Lorenzo Rossi, CEO.

Both Holostem and Newronika are exceptions in the market because these companies are taking their products to final development on their own, rather than letting the later-stage development to third parties. More common is to see Italian drug developers operating B2B models, selling an early-stage development project to a pharma company that will take it through final development and eventual commercialization.

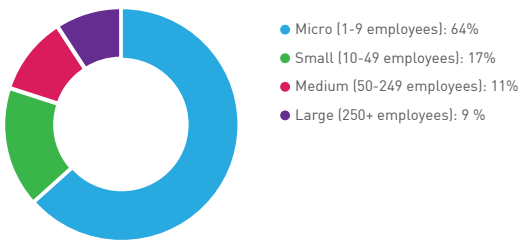
Nerviano Medical Sciences (NMS) Group, a small molecule developer focused on oncological kinase inhibitors, is looking to change this approach, revisiting both its early and late pipeline

strategy after finding itself in a better cash position since being acquired by Chinese company Hafei SARI in 2017. "The acquisition and newly injected financial resources allowed NMS to change its previous business model from that of early out-licensing of products to embarking much more comprehensively in the independent clinical development of our pipeline. We are shifting the business model to carry the project later in the development phase through to PLC (proof of concept) or Phase 2 clinical trial, at which stage we can look for a global pharma partner," said the Group's CEO, Nanding Zhao.
Other drug developers keep all options on the table. "With more investment, we could bring our product to proof of concept in the clinic; the second option is to immediately partner with a pharma company. There appears to be interest from both investors and licensing partners, and we invite those who are seriously interested to join us," said Franco Lori, the CEO of Virostatics. Virostatics' best-candidate for a new class of inhibitors used in the treatment of aggressive cancers is currently in advanced pre-clinical development.

Biotech at a Glance

Number of Firms: 751
Healthcare Focus: 50%
Biotech Turnover: 11,373,674
Total R&D Investments: 1,784,24 8
Employees: 13,24 6

Size Analysis



Source: Assobiotec

The localization of clinical trials

Whereas at the European level, the number of clinical trials has been in decline, Italy is seeing an increase in the percentage of trials conducted in the country. AIFA's 19th National Report on Clinical Trials showed that 22% of all European trials take place in Italy. As in previous years, half of these trials are focused on oncology, but there is also a notable increase in the number of rare disease trials. 31.5% of all orphan drugs European trials are run in Italy.
Even though pharma companies do not need to run a clinical trial in Italy to register their products in the country, running at least part of the product development locally may place the marketing authorization holder (MAH) in a better position during the price negotiation procedure for reimbursed drugs. Laura Crippa, the CEO of RAReg, a company offering market access and regulatory affairs services to pharma companies in rare diseases and oncology, recommends drug developers to include Italy in their clinical trials: "Italy does not only offer state-of-the-art research with highly qualified clinicians who can help with patient enrolment and treatment up to the strictest of protocols, but it is also a large market with a public healthcare system ensuring the best possible care for all patients."
Italy has made great progress in streamlining its bureaucracy and protocols. The country used to have hundreds of local and regional ethics committees, which it narrowed down and centralized under a new Centre for the coordination of Italian regional ethics committees back in 2018. Nevertheless, there are still many duplications in fees that make Italy an expensive destination for activation costs in clinical trials. Local consultancies have proven pivotal in helping smaller players navigate the regulatory field. For instance, Milan-based consultancy Del Corno & Associati works with about 120 clients, mostly SMEs but also some start-ups, who are becoming more eager to, and reliant on, outsourcing their regulatory affairs: "Italy is very particular in terms of project development, regulatory rules and the strategy needed to enter the market, so it is essential to know the market extremely well. For many years, Italian SMEs have preferred to dedicate a specific area for regulatory affairs and pharmacovigilance within the company. However, this mentality is changing in many cases and there are numerous businesses that are outsourcing these services," said Cristina Del Corno, managing director.
During the pandemic, clinical trials became even more challenging. During lockdown, all clinical trial enrolment was stopped except for oncological. During this time, CROs, who were the first affected, looked to digital and remote vists, but GDPR (General Data Protection Regulation) guidelines did not permit data transfers. UK-based CRO Pharm-Olam liaised at the European Commission to relax these data privacy measures but some sites still didn't approve sensitive data exchanges for another 12 months. Today, the remote visit process remains a back-up option, and CROs remain hesitant. "More companies offer home-services for patients, but it is yet to see how the market will react, depending on each country. The idea is to offer greater comfort to the patient, but also minimize data entry mistakes and improve reporting. However, while the world is becoming more digital, some patients are not as digitally-savvy," said Anna Formosa, country manager for Italy at Pharm-Olam.
Opis Research, a CRO with Italian origins but operating globally, has experimented with digital monitoring, but found it not viable when used on an exclusive basis. "The quality and experience entailed by e-monitoring remain incomparable to site, unmediated observation," said Giovanni Trolese, VP and executive director: "There is still more to explore on how to achieve better organization for the running of clinical trials during a time of crisis – and digitalization is only a part of that. Authorities should provide access to sites and support CROs to shorten training times for CRAs, for instance, as well as lending more support to submission processes." ■

Marco Dieci

CEO,
HOLOSTEM TERAPIE AVANZATE

> My vision is to see a single pan-European payer for rare diseases, linked to a database of patients, each with its particular indication.

Holostem was founded in 2008 as the first biotech company fully devoted to ATMPs (advanced therapies medicinal products) based on epithelial stem cells. Can you introduce Holostem to our international audience?

Holostem was created as a spin-off from the University of Modena and Reggio Emilia, together with the partnership of Chiesi. Our concentrated efforts led to the GMP authorization of the facility and the development and registration of Holoclar, the first regenerative medicine product used in limbal stem cell deficiency (LSCD) caused by burns to the eyes. This rare disease affects about 3.3 out of 100,000 people in Europe. The market authorization was received seven years later, in 2015.

Throughout this period, Chiesi used its network to commercialize the product in eight European countries, where it is still present. However, since June 2020, we officialized the transfer of marketing authorization to Holostem in order to ensure greater success of the treatments by offering an integral service with dedicated people, facilitating direct contact of our medical service with clinical centers and physicians during the critical phases of biopsy and implant. Our aim has been to provide a full-package service that supports all the stakeholders in delivering the best therapeutic treatment to patients. By September 2020, we successfully registered the product under our own brand, and this year we also made Holoclar available in the Czech Republic.

Could you help our audience better understand what defines ATMPs?

The big difference ATMPs make is that they have a long-term restorative effect rather than offering a temporary solution. Based on different variables, ATMPs have an efficiency rate of 30% to 50% and are only administered only once or twice, having a life-changing impact.

What is the market size of LSCDs and what is your strategy for reaching this fragmented market?

Every year, about 700 new cases of LSCD are registered in Europe, with around 50 to 100 new patients in each European county, depending on its population size. However, there are many patients who might have suffered an eye injury 20 years ago and they can have the option to see again. As an orphan drug, it is indeed challenging to commercialize the product given the different rules in different jurisdictions. My vision is to see a single pan-European payer for rare diseases, linked to a database of patients, each with its particular indication.

What is the scalability enabled by the GMP stem cell-based cultures facility?

Our current facility could cover 250 patients yearly. To significantly increase our capacity, we need to build a new facility. Holostem's business model relies on one technology platform for regenerative medicine for various applications, so the capacity expansion could also be spared for other indications like hypospadias, which has a larger patient pool. In gene therapy, epidermolysis bullosa is a condition with a devastating impact on the life of the patients and their families; there are about 7,000 cases in Europe, but we can treat only around 100 patients in the EU at the current capacity.

What is the strategy for the rest of your pipeline, including the Phase 3 treatment for the junctional epidermolysis bullosa?

The Phase 3 trials will start in three countries – Italy, Germany and France. To bring this pipeline forward, we are looking for additional investors to speed up clinical trials, registration and commercialization. As one of the few biotech companies with a university on board, we'd like to bring in a third stream as either a buy-out, a venture capital fund, or institutional support who can affiliate in this private-public partnership.

How do you see the bridge between innovative ideas and commercial success in Italy's ecosystem?

In 2015, Holocar was the first drug in its field to receive market authorization, and although we have met all compliance requirements, we have not benefited from government support in the form of a cash refund or discounts for the development activities. The biotech segment in Italy abounds with know-how, yet this know-how is lent in a CMO context. Holostem is one of the few players who develops and also commercializes its products. In Italy, there is a big gap between the lab and ideas hitting the market. ■

Fabio Bianco

CSO
BIO4DREAMS

> **Bio4Dreams is a certified private incubator focusing on early-stage life sciences projects.**

Can you introduce Bio4Dreams and explain its role in the life sciences industry?
Bio4Dreams is a certified private incubator focusing on early-stage life sciences projects. We work closely together with very young start-ups or even wanna-be start-ups, understanding the science and helping structure the project until they are ready for the next stage of industrial or financial partnerships. We have a hands-on approach, offering not only tailored support, but also seed investment.
Our targets are ideas that respond to an existing market need and bring extra-expertise into the sector, rather than the high-risk, high-gain projects. Bio4Dreams started with a focus on advanced therapeutics, diagnostics, medical devices and AI in healthcare, but we are expanding our scope to emerging fields such as green-tech or blue-tech where there is a serious challenge of connecting disparate approaches hanging between different areas of application.

What can you tell us about the life sciences start-up scene in Italy?
There are two factors that inhibit the tech transfer value chain: Firstly, life sciences is a very complex industry requiring specialized infrastructure and matching expertise. Secondly, while Italy is globally recognized as a great hub for scientific research, the science arrives at the tech transfer office too early and is unable to gain the trust of investors. Whereas in countries like the US, universities act as the first links for the tech transfer, this filter is missing in Italy as well as in Eastern Europe where we see a similar fragmented start-up environment. Bio4Dreams intervenes at this stage to build the link between science and industry, but also to support the industry into a cultural change – to engage with start-ups at the science level first, and only later at the commercial level.
Italy's problem is not lack of money, but the fact that funding is not reachable because the project is not structured and presentable enough for investors. Access to angel investors is also tangled in red tape and bureaucracy. Some of the start-ups we work with have binding contracts with early investors that preclude their further development, while others obtained first-round investments and now find it difficult to attract new streams. We need more clarity around the conditions defining each investment so that the investment is equitable and fair for both the start-up and the investor; we also need more clarity around who owns the money and who owns the science.

How is "Innovation Circle" helping structure early-stage start-ups?
Last year, Bio4Dreams created Innovation Circle, a physical space that aims to connect different players across the tech transfer value chain, where start-ups do not ask only for money, but for guidance from their early stage. A project receiving intelligent support early enough has much greater chances to succeed in the market and be more prepared for the next steps.

Can you elaborate on the international program of Bio4Dreams?
We are currently creating a pipeline of start-ups in countries like Slovenia, Hungary, Poland and Finland. Today, we have over 12 sites in Italy and four sites across Eastern Europe. Whenever we identify a good innovation hub with all the ingredients - local players, good science, and good financing opportunities – but with a missing link, we go in and seek to connect the dots.

How has the pandemic influenced global and sectorial collaborations?
The pandemic has brought tremendous opportunities to the life sciences, first of all by bringing down walls, be they geographical or domain-based. It has become very common to create transversal teams, with chemical scientists working side by side with computer scientists, but also to look for human expertise across borders. We signed a partnership with the Pennsylvania Biotech Center, one of the top biotech incubators in the US; we became their life science counterpart in Europe, but also a getaway for European projects to enter the US space.

Bio4Dreams is moving its HQ to the Milan Innovation District (MIND), also managing MIND shared labs. Could you tell us more about this concept?
We are one of the first companies to be moving our HQ to MIND. MIND is a refurbished 1 million m² former exposition area turned into a multi-branded, multi-disciplinary, smart-city innovation hub that expects to gather 60,000 researchers in the next 7-8 years. This is a public-private partnership made of three pillars: a research center, an educational center, and a clinical center. Between these three pillars, there will be an area dedicated to start-up landing, called MIND village. ■

Riccardo Carbucicchio

CEO,
NTC

> We start by identifying unmet medical needs and applying our technological and regulatory expertise to develop new drugs, medical devices and, occasionally, food supplements.

Can you give us a brief overview of Novelty Technology and Care (NTC)?
NTC leverages technology to discover and develop novelty products that improve people's care. We are partnered with around 250 pharmaceutical companies globally, selling our products in approximately 100 countries. Operating a B2B model, we start by identifying unmet medical needs and applying our technological and regulatory expertise to develop new drugs, medical devices and, occasionally, food supplements. Most of NTC's employees are recruited from MNCs, but we have a very young and diverse talent: 70% of our team are women and the average age for our employees is under 40.

What is NTC's current innovation focus in ophthalmology?
NTC operates in selected therapeutic areas, but our biggest focus is ophthalmology. A recent program we are working on is antibiotic resistance, as inspired by the large-scale WHO program. The widespread use of antibiotics in ophthalmology has made several currently administered therapies largely ineffective. NTC has worked intensively to identify antibiotics with the lowest level of resistance with a broad spectrum of action on gram-positive and gram-negative bacteria. We have combined these products with anti-inflammatory drugs that are commonly used in ophthalmology and explored new therapeutic indications. For example, we developed the first fixed combination in eye drops for the treatment of post-cataract patients to be used for only one week after the intervention compared to other options on the market that require two weeks' administration. By reducing this timeframe, we also reduce patients' exposure to antibiotics, we improve compliance and simplicity in drops intake.
We are also finalizing the development of the first fixed combination of an antibiotic and a non-steroidal antinflammatory drug for bacterial conjunctivitis. The combination of an antibiotic with a NSAID has the advantage of providing faster improvement of signs and symptoms. Additionally, we have developed several products with antiseptic properties to reduce the risk of infection in ophthalmic surgery or to treat blepharitis, a very common condition caused by bacteria like staphylococci. NTC also has a large range of innovative products to treat dry eye, and we are the first company to have fully developed ointments with hyaluronic acid. We have also developed eye drops transforming into gel when applied into the eye as a reaction to the change in temperature (in other words, a gel in drops). Finally, we have developed a range of sprays for dry eyes and allergies.

Could you familiarize our audience with some other key products in your portfolio?
For gastroenterology, we have a line of products for irritable bowel syndrome (IBS). However, our most important product is a new drug for patients undergoing colonoscopy. This innovative product aims to clean the patient's colon in a couple of hours in a very simple and efficient way. The product is patient-friendly and easy to take. It is currently completing Phase 3, and we have 1,000 enrolled patients as part of a very large clinical program across several European countries. I expect this product will enter the registration phase before the end of 2021.

How has the pandemic impacted demand for your products, but also the running of clinical trials?
Hospital visits decreased significantly during the pandemic and the number of eye surgeries dropped. Otherwise, patients continued to treat themselves for dry eye or glaucoma, so non-hospital products were not significantly affected. For our clinical trials, we clearly had to navigate many challenges, but luckily, our experienced team reacted fast with the recruitment of patients for our clinical programs as soon as the pandemic started to ease. In this way, we did not suffer any material delays. Moving forward, we expect a growing ophthalmology market as the global population grows, and people's lifespans are also growing.

What are NTC's key objectives in the next 2-3 years and do you have a final message for our audience?
Our main goal is to establish global partnerships for many innovative products and to market a significant portion of our portfolio in 50-100 countries. Currently, our Italian business represents only about 15% of our sales. 70% of our sales are European, and the remaining 30% are outside of Europe. We recently entered two large partnerships in Asia, and we expect China to be an important growth driver in the coming years. ■

Luigi Aurisicchio

CEO,
TAKIS BIOTECH

Together with Rottapharm Biotech, we are developing the only DNA-based SARS-CoV-2 vaccine in Europe.

Can you briefly introduce Takis Biotech to our audience?
Takis Biotech was founded at the end of 2009 by a group of scientists from the Merck Research Laboratories (MRL), where I was leading the cancer vaccine research. Over a decade later, Takis has grown into a 30 people team. Our expertise is genetic vaccination. We started from gene therapy, developing vectors able to express a therapeutic gene, such as interferon, to correct diseases, but then adapted the adenoviral vectors platform from gene therapy to develop cancer vaccines against tumor antigens. We already demonstrated that our genetic vectors can activate a potent, pleiotropic immune response against cancers.

Could you elaborate on your unique expertise in electroporation?
Takis is a pioneer in the in-vivo electrogene transfer of plasmid DNA (DNA-EGT) using electroporation. Electroporation is a technology that permits the entry of the DNA into muscle cells to stimulate the immunological process; this facilitates a greater DNA cell uptake and enhanced protein expression, which translates to a longer-term immune response.
This technology is adapted from IGEA, based in Italy. IGEA uses electroporation for electro-chemotherapy, whereby they inject surface tumors like melanomas with a chemotherapeutic agent which is then electroporated; the chemotherapeutic agent enters the cells, shrinking the tumors in 90% of the cases. We modified IGEA's device for electro-gene-transfer, through which we electroporate the muscle. We can create an "e-gun," a syringe injecting the vaccine and electroporating at the same time with an electric field. We have already started developing this technique for other infectious diseases such as malaria.

What is the potential of genetic vaccines therapies in the treatment of cancers?
When we started working on cancer vaccines, there was not enough knowledge about the immunogenicity of tumor-associated antigens; scientists focused on using molecules that were expressed by both the tumors and the normal tissues, which made it very challenging to channel the immune response to the cancer only - and not the healthy tissue. With the advent of bioinformatics and next-generation sequencing, we can now identify specific antigens found only in tumors and induce a much stronger immune response.

What is the progress in the development of your anti-Covid vaccine?
Together with Rottapharm Biotech, we are developing the only DNA-based SARS-CoV-2 vaccine in Europe; after receiving AIFA's authorization, the CovideVax is now undergoing Phase I clinical trials. DNA-based vaccines do not necessitate cold chain storage and transportation. Another advantage of the vaccine is that it can be administered several times to increase the immunological response thanks to our unique electroporation technique.

Takis is associated with two more spin-offs. Can you tell us more about these companies?
In 2016, we had our first spin-off, Evvivax, which stands for Engineered Veterinary Vectored Immunotherapy and Vaccines, and it uses the same genetic technology mentioned before but applied to animals. Evvivax was born while developing human-focused cancer vaccines: Typically, vaccines are tested in clinical trials on rodents before moving to primates; however, for cancers, there isn't a model in non-human primates on which to test for an antitumoral effect. Therefore, we started using dogs as a model for testing the vaccines because dogs are exposed to exactly the same environmental factors as humans, and they have a genetic predisposition to develop cancers. This made for more real-life, complex, and heterogeneous testing. When we published our first paper demonstrating that our vaccine, in combination with chemotherapy, was able to double the survival of dogs suffering from cancer, many US veterinary practitioners got in touch. This is how we discovered a large market for cancer vaccines in the animal health space and created Evvivax.
Evvivax is also working on a Covid-19 vaccine for animals because cats and minks get infected by the virus.
In 2020, we established our second spin-off, Neomatrix. Neomatrix's specific mission is neo-antigen-based cancer vaccines. The therapeutic vaccine is used in patients with locally advanced or metastatic solid tumors. We have produced the proof of concept in mice and in human biopsies, and we are looking for investors to move to GMP preparation and clinical trials. ■

Lucio Rovati

President,
ROTTAPHARM BIOTECH

> We are scouting for those opportunities that can have a disruptive effect in the field, and that can make a real difference in people's lives.

Can you introduce Rottapharm Biotech and walk us through some recent milestones?
The roots of the company go back to Rotta Research Laboratorium, founded by my father in 1961. It was originally a small laboratory dedicated to the creation of new medications. Progressively, it became a pharma company with a strong focus on R&D, and eventually, one of the first and largest Italian pharmaceutical multinationals.
In 2014, we transferred the company's commercial operation to Meda, a major Swedish MNC later acquired by Mylan. However, we retained what I call the soul of the company: 5,000 m2 of R&D labs operated by 100 scientists. Rottapharm Biotech originates as an R&D spinoff of Rottapharm Madaus.
In the last 12 months, we restructured the R&D business according to three main pillars: The first is concerned with the continuous development of in-house projects. The second is to look for external promising projects and lend support to their development. The last is to collaborate with small biotech companies that already have their own operational capabilities by providing them with our strategic and financial input, for instance by becoming a part of their board.

Rottapharm is currently developing a DNA vaccine against Covid-19 with Takis. How is the development progressing?
We decided to look at something different and not replicate the RNA or viral vector methods that Big Pharma pursued. We found an excellent opportunity with Takis, a biotech firm with sound expertise in the development of DNA vaccines for cancer, quickly adapting their technology for Covid-19. We helped them find the appropriate manufacturing facilities and set up non-clinical and clinical activities. Because this is the first DNA vaccine to be tested clinically in Europe, the regulatory process has been slow, but we should have the preliminary data by the end of August. Today, we are close to completing Phase 1 Studies.
DNA vaccines are relatively underexplored and boast significant advantages. First, DNA information is longer-lasting than RNA genetic information, which means that the possible response from the vaccine could also be more persistent. Also, DNA is a very stable molecule, not requiring a cold chain as opposed to RNA vaccines.
However, DNA is also a bulky molecule, which means it does not enter the cell by itself. We use a technique called electroporation through which we administer a small electrical input together with the injection. This opens some pores on the surface of the cell and allows the DNA to enter and to be translated into the actual protein. Therefore, the procedure of administration is slightly more complicated.

Rottapharm Biotech is focused on rheumatology and osteoarthritis (OA), in particular. Could you update us on your latest research developments?
We have always focused strongly on rheumatology and specifically on OA, one of the most common and most difficult to treat rheumatologic conditions. In fact, we invented the first formulation of glucosamine sulphate, approved in Germany in 1974, and which became one of the most commonly used OA remedies.
We understood that there are different forms of osteoarthritis, caused by separate factors like obesity, inflammation, metabolic derangement, etc., and that a single drug cannot be effective for all kinds of patients. Today we are targeting the phenotypes (subsets) of osteoarthritis through monoclonal antibodies and small traditional molecules. We are also in Phase 2 of a clinical trial for a small molecule, an analgesic called CR4056. This is proving to be very effective against the symptoms of this disease.
While working in rheumatology, we realized that one of our compounds, which originally seemed like an anti-inflammatory agent, actually had an immunological component. Since rheumatoid arthritis is mainly an auto-immune disorder, we developed a compound for this disease called CR6086. We are now developing this compound also in cancer, combining it with immune checkpoint inhibitors, to which some cancers do not respond. Specifically, we are doing a clinical trial in colorectal cancer, combining our compound with immune checkpoint inhibitors.

What are Rottapharm Biotech's priorities in the medium term?
While pharma companies need to be focused on both innovation and commercial activities, we are proud to be completely devoted to the development of new and innovative medications. We are scouting for those opportunities that can have a disruptive effect in the field, and that can make a real difference in people's lives. Rottapharm positions as a link to pharma companies wherever they may be in the world. ■

Franco Lori

CEO,
VIROSTATICS

Taken from a very initial concept, we screened libraries of thousands of drugs to come up with the best candidate: our novel, oral CDK4/6/9 inhibitor, called VS 2-370, is currently in advanced pre-clinical development.

Could you introduce Virostatics?
In the last 15 years, we have worked on developing small molecule compounds with unique activity and safety profiles that respond to unmet needs – in oncology, we typically look at aggressive cancers without a cure or with limited treatment availability; in virology, we also target viruses with high unmet needs or new viruses, including the Corona virus.

How do you split your focus between the two fields – virology and oncology?
Virostatics' legacy comes from HIV/AIDS, where we induced the first case of functional cure – the well-known "Berlin" patient. However, the AIDS market became crowded, so we developed greater expertise in oncology over the years. When the Covid pandemic hit, however, we re-established our virology lab; here, we developed unique expertise in providing testing services for third parties who wish to do in-vitro testing of drugs, biologics, disinfectants or devices, for all SARS-CoV-2-variants and on all surfaces – from solids to liquids.

Could you tell us about Virostatics' pipeline?
We are developing a new class of molecules called CDK4/6/9 inhibitors, used in the treatment of aggressive tumors; our tests show that the new class of inhibitors work in every type of breast cancer that had become resistant to previous CDK 4/6 inhibitors treatments. The current first-line therapy for metastatic breast cancers are in fact the CDK 4/6 inhibitors; however, patients eventually become resistant to this treatment and presently need to switch to the much-more invasive chemotherapy. Taken from a very initial concept, we screened libraries of thousands of drugs to come up with the best candidate: our novel, oral CDK4/6/9 inhibitor, called VS 2-370, is currently in advanced pre-clinical development.

How do you find the drug development climate in Italy?
Italy benefits from a vibrant academic scene, as well as a rich plethora of start-ups, including in the biotech sector. What we are missing is the next step of taking ideas to the market at a large scale. Drug developers like Virostatics are rare, unfortunately. It is difficult to find competent people in this field, but more importantly, what we are missing is an R&D-driven pharma industry. The Italian pharma industry counts a few great names, but we are missing the culture of bringing a drug from pre-clinical to leading the market. This is why we need to seek out partners in the UK, Switzerland, or the US, rather than Italy. While a company like Chiesi might find big investments, Italy lacks investors for the 2-6 million euros capital size. Between big producers, distributors, APIs, proprietary drugs holding Pharmas, and the academia or start-up community, there is a big hole – this is the Achilles' hill of Italian drug development.

Has the pandemic changed mindsets around investing in high-risk pharma development?
One would be tempted to argue that the pandemic created more willingness to invest in addressing health challenges in the future; also, there is a large cash opportunity in Italy, with over 200 billion euros from the EU. Thirdly, we have a prime minister who is well familiarized with the EU mechanisms and knows how to leverage opportunities. But besides these three pluses, we have a cultural minus: we are not used to thinking about long-term investments as we are skilled to facing emergencies. Cultural change is the slowest to occur, which is why I don't expect a dramatic change driven by the pandemic.

What field of research do you think will bring the most promising therapies for cancer?
Gene therapy or precision medicine have received a lot of attention, but I don't expect the next big breakthrough to come from here. Small molecules will continue to surprise us, because the targets are endless and we've only just scratched the surface. Vaccines, both therapeutic and preventive, in combination with AI, could be the next big wave since the discovery of small molecules. We are discovering more of the intricate connections between anatomy, histology, molecular biology, and immunology of cancers; what we are lacking is an understanding of how cancers evade the immune system and how to tackle cancers by inducing an appropriate immune response. The complexity of our immune systems exceeds our brain (collective) capacity to understand how exactly the target interacts with the body's defence system. AI could thus guide the new generation of immunology-based drugs. ■

Giovanni Amabile

CEO,
ENTHERA

> So far, we've raised 35 million euros in a Series A financing, the largest such funding round by an Italian biotech to date.

Enthera was founded to develop first-in-class biologics for autoimmune diseases like Type 1 Diabetes (T1D) and Inflammatory bowel disease (IBD). Could you introduce the company?
Enthera was officially launched in October 2016, and I joined as the first employee in 2018 after the conclusion of the initial pre-clinical work. I was then assigned to generate a clinical candidate to address our target autoimmune conditions and to recruit senior executives. We have made rapid progress over the past three years, and we are now planning for the initiation of our first clinical trials next year. We are delighted to have attracted the attention of several corporate investors who decided to invest in an Italian company for the first time, including Roche Venture Fund and AbbVie Ventures. We are also expanding our research and are currently in the process of opening an early discovery laboratory at the Italian life sciences campus OpenZone.

What is unique about Enthera's scientific approach and proprietary know-how?
Existing therapeutic options currently available on the market for the degenerative diseases that we target, such as T1D and IBD, can only slow down or stop progression, but there is currently no real disease-modifying treatment that can revert the destruction of the organ – whether this is the beta cell mass in T1D or the gastrointestinal mucosa in IBD.
For decades, therapies have focused on modulating the immune system in order to treat these conditions. Enthera takes a different approach by targeting specific pathways that are disrupting the stem cells present in the target organ. To restore the original structure of the mucosa in IBD or the beta cell mass in T1D, you need to re-establish and unleash the capabilities of the progenitor cells that have been lost in the respective specialized tissues. The immune system plays a definitive role in this regeneration, countering the progression of destruction within the organ.
We identified a specific pathway – IGFBP3/TMEM219 – that is disrupted by the immune cells involved in the autoimmune response that underlies disease progression. By rehabilitating this pathway with our candidate (a monoclonal antibody targeting an unconventional apoptosis receptor) we can restructure the original structure of the mucosa in pre-clinical animal models and shut down the autoimmune reaction. In other words, we substitute the inflamed tissue with regenerative tissue, inducing long-term tolerance. We call this approach "regenerative immunology".

Enthera's pipeline consists of one main asset for T1D and IBD, as well as some undisclosed biologics. Can you elaborate on the progression of your pipeline?
Our lead clinical candidate is already in GMP manufacturing, and we plan to begin the first clinical trial with healthy subjects at the beginning of 2022. Next year, we want to continue with at least two other studies, one in T1D and one in IBD, to achieve a significant clinical proof-of-concept. We are also expanding the number of indications to include fibrotic conditions, which are at the intersection between an autoimmune condition and a metabolic disorder. There are no effective treatments on the market for such conditions at this time.

What is your financing strategy and how much investment will be required to bring these therapies to the market?
Enthera is lucky to have some Blue-Chip investors that are very robust and provide significant credibility, as well as financial backing. One of these is the institutional venture capital (VC) fund Sofinnova Partners. Other corporate investors, such as Roche Venture Fund or AbbVie Ventures, not only provide financial assistance, but competence and capabilities in development and manufacturing.
So far, we've raised 35 million euros in a Series A financing, the largest such funding round by an Italian biotech to date. The proceeds will finance at least two clinical studies and the start of production, so that we can obtain tangible clinical data. We will need at least 80+ million euros to bring the product to the market, especially for T1D, for which there is currently no drug approved. Eventually, we will conduct a pivotal worldwide study with the aim to commercialize globally.

How do you find the innovation sector in Italy?
In Italy the focus has previously been on commercial rather than R&D businesses. In recent years, however, several VCs have arrived and are now filling the funding gap between the high level of academic research and the translational part. Italian start-ups are conducting cutting-edge science that can change the course of diseases, and so this could be a great moment for Italy and for academic projects to find the right partners and further research. ■

Anna Formosa

COUNTRY MANAGER,
PHARM-OLAM

> **The core of our business is represented by international trials, as we are recognized as leaders in diseases like warm autoimmune hemolytic anemia (WAHA).**

Pharm-Olam is a mid-sized CRO with a global presence. Could you introduce its activity in Italy?
Pharm-Olam Italy was established in 2004 close to Milan, and in 2009 we moved the office to the Milan city-center. We are a niche player in the CRO panoramic, having established ourselves as key players in oncology, infectious diseases, rare diseases and immunology. The core of our business is represented by international trials, as we are recognized as leaders in diseases like warm autoimmune hemolytic anemia (WAHA). In the past 10 years, we began offering more local studies, important for marketing registration and for players who want to be present in the country but lack the capabilities. Pharm-Olam Italy has doubled its size since 2004, and we have supported over 50 clinical trials in both pharma and medical devices through these years.

What has the pandemic meant for clinical studies providers like Pharm-Olam?
During the lockdown, hospitals were fully engrossed in helping Covid patients, so enrolment for all but oncological trials were put on hold. The timelines agreed with our clients were delayed, nevertheless, we stayed connected with study coordinators and Principal Investigators (PIs), who, in turn, stayed in touch with patients, monitoring treatment compliance or side effects. At this time the sharing of data via remote visits was not possible due to the new GDPR guidelines on data protection therefore we had to follow the study progression via direct communication with site staff.

As the pandemic continued and when there was no immediate sign of the sites opening, we then worked with the EC's to agree on a platform for remote visits whilst maintaining data privacy. However, despite this, some sites did not approve this practice until 12 months later.
In May 2020 hospitals re-opened and our CRAs were able to resume on site monitoring activities. We now also have an approved remote visit process in place with sites as a backup solution should there be another lockdown.

What are some recent demand drivers?
The pandemic has clearly intensified the focus on vaccines, and many companies run vaccine trials in Italy. We support our UK colleagues who are partners in the Phase 3 development of the Valneva Covid vaccine. In Italy, we see higher interest in research, particularly biotech research, offering small companies with one or two molecules the opportunity to enter the market. This is a very lively market, with many ongoing trials and high competition, which drives a high level of quality.

What opportunities does Italy offer as a CRO outsourcing destination?
Between 2014 and 2018, investments in clinical research averaged €750 million per year, with hospitals representing 50% of the beneficiaries. Italy is a very innovative country and its history proves so: Italians were the first to use stem cells, the first genetic therapy was done here, and the first somatic therapy too. Italy also ranks 6th in terms of clinical publications globally, and we have very well-respected opinion leaders. Many clinical trials involve Italy, especially now that the timeline for clearing the regulatory framework is similar to the rest of EU.
With many solutions for endocrinological or cardiological pathologies, biotech companies are focusing more on rare diseases with no existing therapies. Orphan drugs also have a faster access to funds and a wider, less competitive market promise.

How do you manage patient recruitment for rare diseases?
Clinical studies for orphan drugs involve multiple sites with fewer patients, so it is challenging in terms of resources and cost implications. Study design on rare diseases has a huge influence on patient recruitment and mapping the patient landscape is crucial. However, given the potential positive impact that new drugs could have on rare conditions – in some situations, leading to cure – patients are very willing to take part in clinical trials.

How are digital solutions playing a part in clinical research?
More companies, including Pharm-Olam, offer home-services for patients, but it is yet to see how the market will react, depending on each country. The idea is to offer greater comfort to the patient, but also minimize data entry mistakes and improve reporting. However, while the world is becoming more digital, some patients are not as digitally-savvy. Also, regulations do not always keep up with technology. Another emerging trend is that of digital therapies, through which a patient can be monitored remotely by implanting a device that delivers the therapy while the patient is doing normal activities. ■

Laura Crippa

Managing Director,
RAREG

> Our mission at RAReg became to enable market access to rare disease players into Italy.

Can you introduce RAReg and how it came into existence?
RAReg was born in October 2012 out of my personal passion for rare diseases. Our mission at RAReg became to enable market access to rare disease players into Italy. We currently support both Italian and foreign companies coming mostly from Australia, Europe and the US. Our customers are typically SMEs not yet based in Italy or taking their first steps to enter the market. We also assist companies that want to establish marketing and commercial activities in Italy but who do not wish to set up a big organization locally. Many of our clients date back to 2013. The name "RAReg" reflects our dedication to rare diseases, but we are also working in other therapies like multiple sclerosis or oncology.

How is the regulatory environment different for orphan drugs?
Italy has paid close attention to orphan drugs and rare diseases, and the number of orphan drugs that are formally reimbursed in Italy is actually the highest in Europe, though the market access process remains lengthy and cumbersome.
One of the key regulations that were adapted to rare diseases is in the payback system, which sets a budget cap on drug spending; the overspent difference is paid back by pharma players, the amount of the payback depending on whether the product was sold to the retail or hospital sector. Because almost all orphan drugs are acquired by the NHS and hospitals, this budget was consistently overrun. Following considerable industry advocacy, orphan drugs have been exempted from this payback. The difference is paid by players in other therapies, and it becomes a complicated topic when these players are also commercializing orphan drugs. Nevertheless, the exemption has incentivized interest in rare diseases and is an important social contribution to rare disease patients.
Another regulatory difference concerning orphan drugs is a shorter timeframe in the PNR (price and reimbursement procedure) of 100 days compared to the 180 days for standard drugs. However, the legislative stipulation does not necessarily reflect the reality, and the process remains lengthy before an agreement is found: companies seek to maximize their return on investment, while AIFA does its duty to negotiate a lower price for patients. Also, AIFA reviews dozens of submissions every day, and it can take months to understand the therapeutic effect of each and the clinical evidence, especially for conditions that are not very common. This timeframe is also slowed down by the lack of possibility for early discussion between companies and AIFA before they submit a dossier, to predict and avoid potential challenges. For these reasons, the 100 days' timeline is a nice thought, but difficult to execute.

How do you observe market behavior and interest in rare disease clinical trials in Italy?
If we look at the AIFA reports on clinical trials, we can see a clear increase in the share of rare disease clinical trials over the years. I would strongly recommend drug developers to include Italy in their clinical trials, not just because of Italy's capabilities in offering state-of-the-art research with highly qualified clinicians who can help with patient enrolment and treatment up to the strictest of protocols, but also because Italy is a large market with 60 million people and a public healthcare system ensuring the best possible care for all patients.

What are RAReg's priorities in the next 2-3 years?
Our top priority is to develop our added-value expertise even further. Related to this, we want to establish a more formal business development and communications strategy with an assigned specialist in this field.
Our second goal is to continue providing top-quality services to our customers through our network of excellent partners. Throughout the years, we have established great partnerships in advocacy, communication, government affairs and tenders. We seek quality, not size, so we build our know-how through these strong relationships rather than bringing it in-house.
Finally, I'd like to see RAReg becoming a benefit company that makes a contribution to society while still working for a profit. More than the title of a benefit company, I want the essence of RAReg to be that of a B-corp, so I will dedicate more time and effort to this matter in the months to come.■

Therapies in Focus

RARE DISEASES

Approximately 8,000 diseases, that is, the majority of existing diseases, are considered "rare" and have an incidence lower than 1 in 7,000 people. Fewer than 1,000 of these diseases are documented with minimal scientific knowledge, and only 5% of them have an effective treatment. This huge blind spot of pharmaceutical research has started to receive more interest, and it is one of the biggest opportunities for innovative drug developers to break into the market and make a real difference, provided they can withstand the challenges associated with orphan drug discovery and commercialization.

Italy formally reimburses more orphan drugs than any other European country, according to specialist consultancy focused on rare diseases, RAReg. Also, there has been an upward trend in the number of clinical trials for orphan drugs in the country, and the percentage of advanced therapy products (ATMPs) is growing at 11% in Italy, compared to the global average of 4.7%.

These numbers suggest a greater interest in the market for developing and commercializing orphan drugs. Large Italian pharma company Recordati has been running a rare disease division ever since 1990, and other leading companies are officializing this interest; in 2020, big Italian pharma Chiesi inaugurated the Chiesi Global Rare Diseases with a headquarter in Boston. The company was already marketing Lamzede, a drug for an ultra-rare genetic condition called Alpha-mannasidosis.

The highly fragmented, incredibly heterogeneous and loosely competitive rare disease sector gathers a large space of unmet medical needs that smaller developers can tap into, though the challenges are even greater for smaller companies. Low profitability prospects have precluded more pharmaceutical interest in this field, despite the overwhelming medical need. Giovanni Sala, the general manager of Medac Pharma explained the investment and the number of clinical trials is as high, if not more, as for high-incidence diseases: "This issue cannot be left on the shoulders of pharma companies alone. With regulators, we should jointly find a rewarding system to enable pharma companies to recover their investment made to find optimal treatments for small groups of patients. The orphan drug status currently offers additional market protections, but more innovative and creative rewarding systems must be jointly identified."

Besides running a special 500 million euros fund for orphan drugs reimbursement, Italy has endowed the "orphan" drug status with different protections in a bid to incentive research in this space. For example, orphan drugs are exempted from the payback system. However, Laura Crippa, the managing director of RAReg, commented this has led to a complicated situation in which the difference is paid by other commercial players operating in different therapies, which becomes even more problematic when these players also commercialize orphan drugs; in other words, they'll pay themselves the discount that the government is granting. The other special exception for orphan drugs is a shorter price-and-reimbursement procedure timeframe, which is 100 days long versus the standard 180 days. Crippa again clarified how this looks like in practice: "The 100 days' timeline is a nice thought, but difficult to execute. The process remains lengthy before an agreement is found, because companies seek to maximize their return on investment, while AIFA does its duty to negotiate a lower price for patients. This timeframe is also slowed down by the lack of possibility for early discussion between companies and AIFA before they submit a dossier to predict and avoid potential challenges. Early dialogue would surely help the process."

What slows down the approval process is also the sophisticated nature of the medicines and the diseases themselves, many having no close precedent or similar counterpart in the market. AIFA reviews dozens of submissions every day, and it can spend months to understand both the unique disease and the presented clinical evidence and therapeutic effect. For example, Holostem received the market authorization for its Holoclar therapy for limbal stem cell deficiency (LSCD) seven years after starting development.

When approved, another challenge comes from market strategy and connecting a very disparate group of patients. For example, LSCD has an incidence of 3.3 out of 100,000 people in Europe, which translates to about 700 new cases every year in Europe. However, there are many other patients who may have suffered the condition ten or twenty years ago, and who can have a chance to see again. "The big difference ATMPs make is that they have a long-term restorative effect rather than offering a temporary solution. Based on different variables, ATMPs have an efficiency rate of 30% to 50% and are only administered only once or twice, having a life-changing impact," said Marco Dieci, the CEO of Holostem.

Dieci's vision is to create a pan-European, single payer for orphan drugs and bring these patients together. Operating from a single pocket would centralize and consolidate the European rare disease market. ■

Cancer therapies

If rare diseases are one of the least researched pharmaceutical territories, cancers are at the other end of this spectrum: Over 34% of all pharma assets under development are related to oncology, estimates PwC, and the top ten oncological drugs are blockbusters selling over US$1 billion each year. Causing one in six deaths (according to the WHO), cancer is one of the biggest killers of the 21st century, and finding the right treatments one of the biggest pursuits of the pharmaceutical industry.

The European Medicines Agency (EMA) recommended 97 drugs for approval across different therapies in 2020. Of these, oncology led the charts with 21 recommendations. EMA marked as "outstanding contributions to public health" three new oncological substances: Blenrep (by GSK), an ATMP used in patients with relapsed and refractory multiple myeloma; Rozlytrek (by Roche), used for solid tumours with a specific kinase gene fusion; and Tecartus (by Gilead), a cell therapy for a rare cancer with relapsing symptoms after various lines of treatment. The focus on rare cancers can also be seen with Menarini, who recently came in possession of ELZONRIS (tagraxofusp) after acquiring its developer, Stemline Therapeutics. ELZONRIS is a monotherapy used as a first-line treatment of plasmacytoid dendritic cell neoplasm (BPDCN), an aggressive blood cancer. Menarini announced at the beginning of 2021 that it received EMA marketing authorization, the drug becoming the first approved treatment for BPDCN patients in Europe.

These examples offer a snapshot of the variety and complexity of what are summarized as "cancers," but which exist in over 100 different types, according to the US National Cancer Institute. The range of therapeutic approaches is just as varied, including chemotherapy, hormone therapy, immunotherapy, radiotherapy, stem cell transplant, targeted therapy, and of course surgery.

Small molecules

Italy has the highest cancer survival rate in Europe, according to the "State of Health in the EU" 2019 report. Coming from a culture of excellent cancer research and medical treatment, Italian innovators are energetically driving forward different oncological therapies.

One of the largest companies in oncological kinase inhibitors, Nerviano Medical Sciences (NMS) Group has been a pioneer in the science since the mid-1990s. "Kinases, over 1000 of them, are the largest classes of enzymes and they are involved in the cell cycle, including the oncogenesis - or the malignant proliferation of cells. Therefore, kinases control the body's inflammatory and immunological reactivity by controlling the gene expression. Our kinase platform comprises more than 100 biochemical assets," shared Nanding Zhao, CEO of NMS Group.

Image courtesy of Itel.

Kinase inhibitors are one of the most established weapons in the battle with cancers, gaining traction at the same time as precision medicine. The FDA approved 37 kinase inhibitors for the treatment of malignancies, and another 150 are in clinical phase.

Also working with small molecules, but this time with a different type of inhibitor, Virostatics is developing a new class of CDK 4/6/9 inhibitors for breast cancer patients who no longer respond to the first-line therapy, the CDK 4/7, in metastatic cancers. Virostatics' candidate is an oral drug called VS 2-370 and is in advanced pre-clinical work.

Small molecules are incredibly versatile with a high number of potential targets that are still little understood, but the next wave since the discovery of small molecules should come from vaccines combined with AI, said Franco Lori, the CEO of Virostatics: "We are discovering more of the intricate connections between anatomy, histology, molecular biology and immunology of cancers; what we are lacking is an understanding of how cancers evade the immune system and how to tackle cancers by inducing an appropriate immune response. The complexity of our immune systems exceeds our brain (collective) capacity to understand how exactly the target interacts with the body's defense system. AI could thus guide the new generation of immunology-based drugs."

AI is gradually becoming an important factor in the drug discovery process. Recently, UCB expanded its partnership with Microsoft to deploy AI for its discovery pipeline. Pfizer also partnered with Concreto HealthAI to advance work in precision oncology, while Bayer collaborates with UK-based AI drug discovery company Exscientia in cardiovascular and oncology drug discovery. AI and machine learning platforms can speed up the search for a drug candidate and enable much better customization according to different factors, genetic or otherwise.

Genetic vaccines

Alongside developments in AI, research in immunogenicity has also made substantial progress. Luigi Aurisicchio, the CEO and founder of Takis Biotech, explained: "When we started working on cancer vaccines, scientists focused on using molecules that were expressed by both the tumors and the normal tissues, which made it very challenging to channel the immune response to the cancer only - and not the healthy tissue. With the advent of bioinformatics and next-generation sequencing, we can now identify specific antigens found only in tumors and induce a much stronger immune response, comparable to vaccinating against a virus. Genetic vaccines have enormous potential."

The science of genetic vaccines is also benefiting from the breakthroughs achieved during research for the coronavirus. Before the pandemic, there were no vaccines using adenoviral vectors or messenger RNA technology outside of some small-scale clinical trials in oncology. With billions vaccinated today, these technologies have been given a vote of confidence and can be extended to cancers.

Proton Therapy

Though Italy benefits from top-class cancer treatments, the infrastructure for some select therapies is missing. Proton therapy is one of the most advanced and efficient forms of radiotherapy, but the high equipment costs have constricted wide-scale development. While in the US there is one proton therapy for every three million people, Italy has a total of two machines – that is one for every 30 million people, with a third machine under construction. Italian company Itel Group set out to change this.

Itel is an Italian leader in the medical and clinical engineering fields. In 2015, it obtained a 15 million euros grant from the European Investment Bank and created LinearBeam, a spin-off focused on creating a proton linear accelerator used in proton therapy against cancers. This would be the world's first proton therapy system based on a P-Linac machine (a linear accelerator of protons); the technology would not only be cheaper compared to a typical proton machine (which can cost up to US$150 million), but it would also be more effective. The prototype is currently pending validation having been transferred to the first oncological center in Italy.

The opening of this facility could make a big difference to Italian patients, proton therapy being both more effective and less invasive compared to traditional radiotherapy: "Traditional radiotherapy works by delivering a dose of electrons or photons to the tumor; however, tumors are typically located in the center of the body, and thus more distanced from the electron input, requiring a higher dose to reach the target. The passage of healthy tissue between the target and the electron is therefore also affected, while there is also a 50% probability of a returning tumor. In proton therapy, the difference is made in the physics of the particles because 100% of the protons' energy is delivered 30 cm away from the beam, the doctor deciding precisely where the proton releases most of its energy burst. This point is called the Bragg Peak. The exact target causes minimum harm to nearby tissue, and a lower dosage is required," said Michele Diaferia, CEO, Itel Group. ■

Cancer diagnostics and AI

Despite the concentrated pharmaceutical and medical efforts, a cure for cancer has yet to be found. However, the availability of different therapies together with better diagnostics have led to improved survival rates for many types of cancers. At the same time, longer lifespan expectations also mean that more people are diagnosed with cancer than at any other time in history. Early detection and diagnosis are essential in completing the circle of better treatment, better survival chances, and better quality of life. These factors have made cancer diagnostics a booming industry. Growing at a CAGR of 11.5%, the global cancer diagnostics market is projected to reach US$ 26.6 billion by 2026.

One of the biggest trends impacting the diagnostics market, both in-vitro and clinical, is the use of AI and digitalization. Gastrointestinal (GI) pharma leader Cosmo Pharmaceuticals has introduced the first AI-enabled device that can detect colorectal polyps during a colonoscopy. This is the first medical device the company launched, though Cosmo has been very active in the field of diagnostics through its pharmaceutical offer, the company owning a unique Multi-Matrix Technology (MMX Technology), which allows tablets to dissolve evenly across the length of the colon's lumen to improve diagnostic conditions.

Cosmo's CEO, Alessandro Della Chà, thinks AI will be taking over the world of diagnostics: "AI can perform the tasks of a highly qualified and skilled physician without getting tired or becoming prone to mistakes. When a lesion in the colon is sent to the histopathology lab, the physician visually analyses the sample to determine its nature. Going forward, this task will clearly be performed more effectively by a computer with less likelihood of error."

A similar dynamic takes place in the cytology space, where pathologists are more and more replaced by digital pathology. Cytology is the part of cancer diagnostics engaged with looking at a single cell type, reading slides on a microscope to identify abnormalities and cells indicating a tumoral presence. The challenge is that many countries, especially in Africa, have no active pathologists, and more developing countries will see the number of practicing pathologists halved in the next five years. Meanwhile, patients in developed countries struggle with long waiting times to get their diagnostic test results back after a test.

Florence-based Hospitex, a supplier of lab instruments for cytology, comes to the market with an offer of digital pathology, which combines digitalization and software to make an interpretation on the slide. The company's CEO Francesco Trisolini explained how this technology differs from traditional cytology: "Our technology has an efficiency factor of 10 times higher than the conventional method and we can return the results within 24 hours."

Image courtesy of Cosmo.

On the other side of cancer diagnostics, histology, the study of the entire block of tissues in samples like biopsies, is also shaped by AI. Integrated Systems Engineering (ISE), a leader in tissue microarray (TMA) technology, has recently received financing from the European Commission for a project that sees the full automation of Tissue Microarray workflow using AI and deep learning algorithms in order to bring the technology in diagnostics. Pasquale de Blasio, ISE's CEO, explained how this works: "Typically, a histology slide is made from a surgically resected biopsy sample embedded in paraffin and sliced with a microtome. The pathologist examines the slide studies and the cancer cells in order to make a diagnosis. This process is repeated for all histology slides. The new platform will perform quantitative visual imaging of histology slides, select the area of interest (enriched with cancer cells) and core this section to create the TMA block. The TMA gathers the tissues (selected by the pathologist) into one block (an array) and >400 spots can be placed in a single TMA slide, allowing simultaneous analysis using the same histology conditions."

The improved technology would be of particular value in diagnosing rare cancers; to identify a rare cancer that affects 5% of the population, the pathologist has to conduct about 100 analyzes, but the TMA can help identify the 5% incidence in a single analysis. ■

Pasquale de Blasio

Founder,
INTEGRATED SYSTEMS ENGINEERING (ISE)

> **The first objective is to continue to develop our TMA technology and move it into diagnostics; to do so, we want to intersect with a commercial and/or financial partner.**

Could you introduce ISE to our audience?
ISE was founded in 1986 and will celebrate 25 years of operations in 2021. ISE runs two business lines: The first line is focused on bioengineering, specifically on the development of laboratory instruments; ISE manufactures the Galileo TMA platform, a leader in tissue microarray (TMA) technology (www.isenet.it). Recently we were selected (16/197) by the DIGI-B-CUBE (financed by EU) for the Innovation Voucher titled: Deep-Learning based Techniques for Precision Tissue-Cell Microarray Processing. This project aims to bring the TMA technology from research laboratories to diagnostics by introducing full automation of the Tissue Microarrayer workflow and Artificial Intelligence (AI) based on deep-learning algorithms. This new platform will perform quantitative visual imaging of histology slides, select the area of interest (enriched with cancer cells) and core this section to create the TMA block.
The second line relates to human stem cells research (hiPSCs) and related services, including organoid and spheroid generation and characterization. These activities are based on our long experience in the Biobanking field. In the late 90s, we joined the International Society for Biological and Environmental Repositories (ISBER) and in 2004, we organized the first ISBER International meeting in Perugia, Italy. In 2010, we established the European, Middle East and African Society for Biopreservation and Biobanking (ESBB) where I was the Founding President.

Could you explain better the potential of introducing AI into the TMA and what this upgrade could mean for digital pathology?
TMA is a technology used mainly in research laboratories but in the future, it will also be used for diagnostic application. To achieve this goal, it is necessary to develop a fully automated TMA workflow, integrated with AI and deep-learning algorithms able to perform quantitative visual imaging of the histology slides. Typically, a histology slide is made from a surgical resected biopsy sample embedded in paraffin and sliced with a microtome. The pathologist examines the slide studies and the cancer cells in order to make a diagnosis. This process is repeated for all histology slides. The TMA gathers the tissues (selected by the pathologist) into one block (an array) and >400 spots can be placed in a single TMA slide, allowing simultaneous analysis using the same histology conditions. This process is particularly important for rare cancers where you need to analyze a large number of patients to detect a small percentage of the population. As an example, if the rare cancer affects 5% of the patients, the pathologist needs to conduct 100 analyses. Instead, he can identify the 5% incidence in a single analysis.

Could you tell us about the availability of biobanking resources in Italy?
In Italy there are two private service providers – Isenet Biobanking, a business which ISE sold to Air Liquide in 2018; and BioRep, which we founded in 2003. I was also involved in the development of Neuromed Population Biobank located in Pozzilli, which collects and studies genetic factors of Molise region selected population. The Moli-Sani biobank contains about 1 million samples stored at -196°C. All other Biobanks are public and part of the BBMRI network.
During the pandemic, biobanks froze operations, but those that focused on Covid-related materials have a great opportunity because they hold valuable materials for pharma companies. Moreover, the ISO 20387 regulation passed in 2018 changed the accreditation system for biobanks. Private biobanks that are ISO 20387 accredited have a great opportunity to stand out. The biggest challenge for private biobanks is to stay sustainable.

ISE recently relocated to the OpenZone complex in Bresso, Milan. What advantages does this offer you?
OpenZone represents a micro-ecosystem in the life sciences sector, many of the companies present here having worked with us in the past. I believe this is the right environment to create synergies between different players, but also to test new ideas – because in research, exchanging and trying out ideas with others is essential. The complex is growing fast; this year, we count over 800 people, but by next year, 1,200 are expected to work here.

What are your main objectives for the future?
The first objective is to continue to develop our TMA technology and move it into diagnostics; to do so, we want to intersect with a commercial and/or financial partner. Though we sell our instruments to the biggest hospitals around the world, ISE's weakness is the lack of a good distribution network. The second objective is to build a biobank of organoids – continuing our expertise as thought leaders in this field. ■

Alessandro Della Chà

CEO,
COSMO PHARMACEUTICALS

Cosmo Pharmaceuticals is a global leader in the gastrointestinal (GI) space, including IBS, colonic infections and colorectal cancer (CRC), and our goal is to increase the effectiveness of CRC detection.

Can you introduce Cosmo Pharmaceuticals and highlight the evolution of its product offer?
Cosmo Pharmaceuticals is a global leader in the gastrointestinal (GI) space, including IBS, colonic infections and colorectal cancer (CRC), and our goal is to increase the effectiveness of CRC detection. Our first drug Lialda (Mesalamine), licensed to Shire (Takeda), sold almost as much as a blockbuster: US$1 billion/year in the US. Since then, we have constantly introduced further innovations, like a new drug using budesonide as an active ingredient against the most severe ulcerative colitis, as well as an antibiotic for colonic infections. We did not shy away from the area of medical devices either: Our MethalyneBlue MMX is the first drug used in colonoscopy to detect CRC, while our GI Genius is the first AI-enabled tool to detect colorectal polyps.

What does your MMX Proprietary technology entail?
The Multi-Matrix Technology (MMX Technology) is a technology allowing tablets to progressively unfold during the colonic tract to ensure the uniform and thorough dispersion of the active ingredient across the length of the colon's lumen. This is an important innovation because, traditionally, delayed-release formulas would simply release the API in the initial part of the colon. Our technology allows patients to receive the full colonic coverage with fewer tablets, while favouring absorption at the colon's level, rather than dispersing the API in the stomach or small intestine. Each of our products has a different MMX formulation, and the approach varies depending on the active ingredient used. MethyleneBlue MMX is an example of our latest drug manufactured with the MMX technology, approved in Europe in 2020.

GI Genius is the first AI tool for the detection of lesions during colonoscopy. How is the product performing in the market?
The progress of GI Genius is much faster in the US than in Europe because the US healthcare system is mostly private, unlike in Europe.

How do you see the evolution of AI in the diagnostics space?
AI will completely take over diagnostics because it can perform the tasks of a highly qualified and skilled physician without getting tired or becoming prone to mistakes. When a lesion in the colon is sent to the histopathology lab, the physician visually analyses the sample to determine its nature. Going forward, this task will clearly be performed more effectively by a computer, with less likelihood of error.

Winlevi is a very innovative acne product marketed by Cassiopea. Why is this technology unique?
Winlevi is a very innovative hormonal therapy. This is a first-in-class drug and the first topical androgen receptor inhibitor. When it penetrates the skin, the active principle degrades into dehydro testosterone, which is a hormone produced by the body. This means that the drug does not create any hormonal imbalance for the patient. Winlevi operates at the root cause of acne, which is the inflammation of the pore in the skin and is extraordinarily safe. The product received FDA authorization in 2020 and has been very well received in the market so far.

What do you make of increased investor appetite in higher-risk pharma, in light of the pandemic?
The current appetite for high-risk ventures comes from the fact that there is high liquidity in the market, so investors do not mind taking risky bets. However, this environment will soon change, and investors will search for safe havens and companies that can generate long-term revenues with lower risks.
In the pharmaceutical industry, we see that the value of companies increases with the publication of promising clinical results; when the final results are confirmed, the share price actually tends to drop.

Cosmo Pharmaceuticals recently started trading on Xetra. Can you briefly comment on this update?
We were already traded on the Frankfurt Stock Exchange (DAX) besides the Swiss Stock Exchange (SIX). We wanted to join the main platform to improve the overall liquidity of the shares and the direct outreach to European investors.

Can you highlight some medium-term objectives?
Our goal for the next 12-18 months is to ensure that GI Genius gets full traction in the US market. Yearly, about 32 million colonoscopies are performed in the US and EU, and we address these needs with our offer of GI Genius, Methylene Blue MMX and Eleview. ■

Innovation highlights: Italian new developments in different therapies

Ophthalmology

"A recent program we are working on is antibiotic resistance, as inspired by the large-scale WHO program. NTC has worked intensively to identify antibiotics with the lowest level of resistance, with a broad spectrum of action on gram-positive and gram-negative bacteria. We have combined these products with anti-inflammatory drugs that are commonly used in ophthalmology and explored new therapeutic indications."

- Riccardo Carbucicchio, CEO, NTC Pharma

Aesthetics

"The patented Hyaluromimethic technology allows the modified hyaluronic acid (HA) to persist more in the body because the body takes longer to recognize it and dissolve it; this will last up to five times longer than regular HA. In addition, lipoic acid present in some formulations based on our technology stimulates collagen and elastin, enhancing a natural biological effect. The modified HA will be used in aesthetics and osteoarthritis, in both injection and topical form. Aesthetics is a US$20 billion market registering double-digit growth, so this is where we see the greatest opportunity for escalated growth."

- Marco Mastrodonato, Founder and CEO, BMG Pharma

Dermatology

"Many of our products contain nicotinamide, a water-soluble amide form of niacin or vitamin B3, which is found in fish, eggs, poultry and cereal grains. This molecule stands at the basis of many of our formulations and medical devices but is also used in sunscreen products; the presence of nicotinamide creates a value-added element and a differentiating point for our products. Nicotinamide has a soothing and therapeutic effect on the skin, helping with conditions like acne, rosacea, blistering, or atopic dermatitis."

- Massimo Montironi, CEO, IDI Farmaceutici

Anti-inflammatory

"We launched a patented diclofenac mouthwash indicated for sore throat and gingivitis, which is both our strongest prospect and greatest success story to date. Diclofenac is the single most-prescribed anti-inflammatory agent in the world, and is currently available in virtually every possible form except as a mouthwash, as this API is absolutely insoluble and strongly bitter. These two technical problems are overcome by our patent, which allows both crystal-clear solubilization and perfect palatability; also, solubilization is attained without alcohol. Hence, our mouthwash is not only the only one with diclofenac, but also the only anti-inflammatory solution without alcohol, two striking USPs that place our technology a cut above competitors. Last but not least, the approved OTC indications are quite ample: sore throat, gingivitis and pain related to dental procedures."

- Alessandro Casero, CEO, Farmaka

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