



Annual  
Report  
2015  
ENGLISH

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 **Chiesi**

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# #01



## RESULTS AND OUTLOOK

Message from the Chairmen

The CEO's analyses

Key events in 2015

Mission

Key financial results

Board of Directors and Board of Auditors

Executive Committee



# The Chairmen's message

Alberto Chiesi  
*Chairman*

Paolo Chiesi  
*Vice Chairman  
and R&D  
Director*

Eighty years are an important milestone that no organisation takes for granted. In 2015 the Chiesi Group celebrated this anniversary, demonstrating year after year its ability to develop innovative solutions that have enabled it to adapt to ever-changing scenarios. The company has such a long story that its current workforce is made up of people with widely diverse ages and experience. This represents a resource in which enthusiasm, innovative vision and high levels of seniority all feature within the working groups. International development has at the same time enhanced collaboration between professionals from very different cultures yet with shared values, such as the centrality of people, striving for excellence and entrepreneurial spirit. This ensures a plentiful supply of ideas, which are needed to find original solutions for the increasingly complex problems arising in the pharmaceutical market.

## Changing scenarios

One of the phenomena likely to alter the pharmaceutical scenario is the increasingly significant role played by market forces in the evaluation of a drug. The conditional approval regulation, introduced by the EU in 2006, tends to accelerate access to innovative products and is particularly beneficial in the case of rare diseases. On the other hand, it requires companies to provide additional clinical evidence after marketing has begun, not only to support the efficacy and tolerance of the new product but also its added value compared to competitors already on the market.

In the last decade information technology has also been applied in the management and monitoring of several chronic diseases, for example asthma and COPD. This is achieved using an online device which is able to transmit parameters such as treatment efficacy and patient compliance to doctors. Aside from their particular use, clinical data gathered in this way tend to amass such a large volume of information that specific analytical technologies and methods are often required to obtain its added value. Although this analysis raises completely new issues of an IT and ethical nature, these data sources represent a new resource whose use is destined to characterise the future evolution of the world of healthcare.



## 2015 results

Three numbers effectively summarise the trend of the Group's activities during 2015: its turnover, which reached €1.467 billion; its source, over 80% of which originates outside the domestic market, and the work-

force, which exceeds 4,500 people. This data indicates that the company is growing (+9.4% on 2014), is increasingly international and has a strong focus on enhancing the value of human resources, which it considers the driving force behind its development.

## Markets

Europe, where the Group is well-established, achieved positive results: Italy, aside from the loss of Provisacor, has grown in a stagnant market; the UK has benefitted both from high levels of sales and the favourable sterling exchange rate. The Netherlands, Austria and the CEE countries, and Greece have gone into double figures. Newly-created Chiesi Nordics has also had an extremely encouraging start, whilst sales have increased in a satisfactory way in France and Germany, as well as in Spain, although to a lesser degree due to the general economic situation.

The Russian and Brazilian markets have been strongly influenced by fluctuating exchange rates, and Turkey has also partly been affected. On the Chinese market, demand slowed significantly in the second half of the year because of the domestic situation.

The US market has achieved significant growth partly thanks to the favourable exchange rate and Mexico also ended the year positively. Moreover, exports showed a favourable trend, particularly in the Middle and Far East.

## Major investments

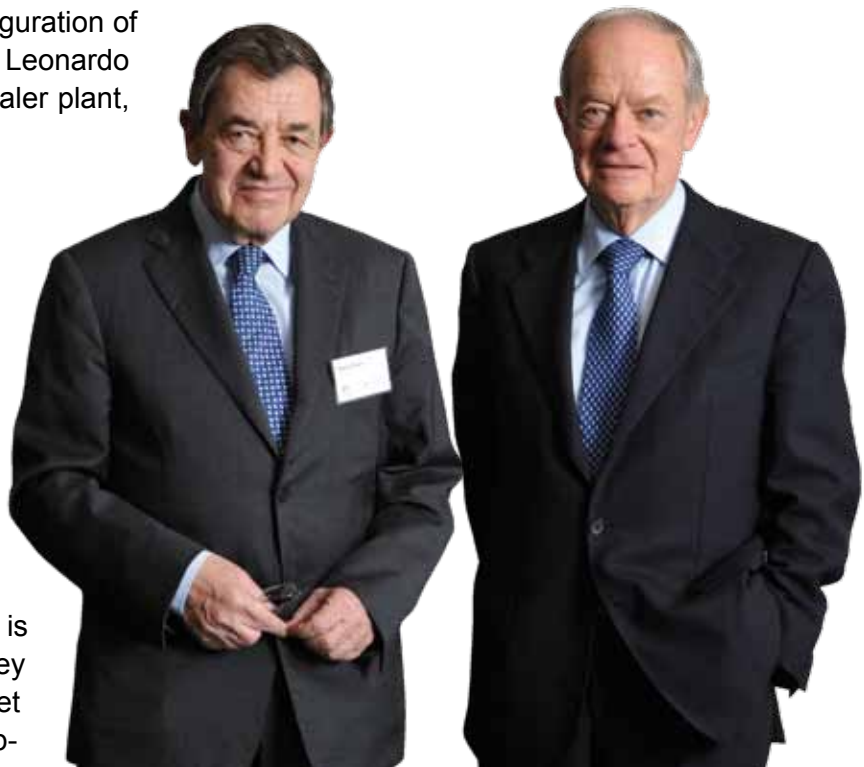
2015 was a year in which significant investment was made in registration trials for the triple association and, to a lesser extent in those for velmanase alfa. In addition, three new projects in the respiratory field have made good progress in the pre-clinical phase and the first clinical trials are expected to begin in 2016.

It was likewise an important year for Industrial Operations, with a number of key events including the inauguration of the new Curosurf production plant at the San Leonardo site and the completion of the Dry Powder Inhaler plant, now fully operative, in Blois, France.

## Product trends

Foster, the Group's main product, achieved a turnover of €492 million, confirming its continued popularity with doctors and patients. Curosurf has further increased its market leadership for the treatment of respiratory distress syndrome in pre-term neonates, whereas Clenil, the company's very first respiratory drug, has maintained its position in all of its markets.

Among the new products, Envarsus, which is indicated for the prevention of liver and kidney transplant rejection and is already on the market in several European countries, has recently ob-



tained price determination in Italy. Last January, treatment with Holoclar, approved by the EMA for corneal reconstruction following serious burns, was used on its first patient. In 2015 Glybera, indicated for the treatment of pancreatic lipoprotein lipase deficiency (LPLD), was also successfully used to treat the first patient in Germany.

## Main activities in 2015

The forecasts made in the 2011 – 2018 strategic plan have mostly been reached, thus confirming the reliability of the development method adopted. The new plan, which will take the company to 2025, is designed to gradually update the Group as a whole.

Particular focus was made on staff exchanges organised between the Italian head office and the affiliates: this has ensured that Chiesi's key values are spread throughout the entire Group and promoted international training for new managers.

The implementation of the SAP system has continued with roll-outs in Austria, including the CEE countries and Brazil. The significant changes made to the management of the processes, supported by adequate training and communications programmes, are proving to be an effective tool for the application of common working standard at all of the affiliates.

## Prospects for 2016

Key events within research and development activities will be EMA submission for the triple association and velmanase alfa.

Aside from the internal research and development of its drugs, the Group is also interested in opportunities for the potential acquisition of organic products indicated for the respiratory field.

For the special care area, and neonatology in particular, Chiesi aims to become a reference supplier for hospitals, offering a range of combined products and services.

Glybera, the first gene therapy drug registered by the EMA, will be made available to some European patients currently eligible for its use. Launches for Holoclar and Foster 200 µg, indicated for cases of severe asthma, are also imminent.

In order to meet the numerous challenging objectives for 2016, the company will once again rely on both its management and all the people within Chiesi, in the awareness that their commitment and skills form the basis for its innovative results and growth achieved in the past eight decades.



## The CEO's comment

2015 was characterised by outstanding sales: turnover reached €1.467 million (+9.4%), almost into double digit growth. The Group also achieved a positive result from a financial perspective, in particular taking into account further investment in Research and Development, with the EBITDA standing at €407 million (+ 9.4% on 2014).

Investment in Research and Development went up by nearly 30%, exceeding 20% of total sales. This additional investment in innovation was made possible thanks to an overall increase in efficiency, based on constant monitoring of selling, general and administrative expenses (SG&A) and a significant improvement in the cost of goods sold (COGS).

Ugo Di Francesco  
CEO or Chief  
Executive Officer

## The Group's products

Foster generated sales of €492 million, with an increase of 19.7% on the previous year. Sales of Curosurf were in excess of €200 million, up by 14.4% on 2014, confirming world leadership among surfactants. Clenil has also grown, increasing sales by value by 2.9% and generating turnover in excess of €176 million.

In line with the Group's strategic objectives, products dedicated to special care, including Cardene in the USA, have increased their share of the Group's turnover to an impressive 26.8% on total sales.

Seen from a geographical perspective, the turnover generated outside the domestic market is in excess of 80%, further highlighting the international dimension of the Group. In spite of unfavourable conditions and several price cuts for key products, the European markets were on average up by 5.2% in terms of turnover, equivalent to 3.2% in local currency.

Currency fluctuation clearly had a significant impact on results in some of the most important emerging markets: for example in Russia, the devaluation of the Rouble partially eroded turnover growth, which was up by 13.5% in local currency. The situation was similar in Brazil, Turkey and, for different reasons, China, Pakistan and Mexico. Nevertheless, the emerging markets overall were up by 11.7% in local currency on 2014.

## Research and Development

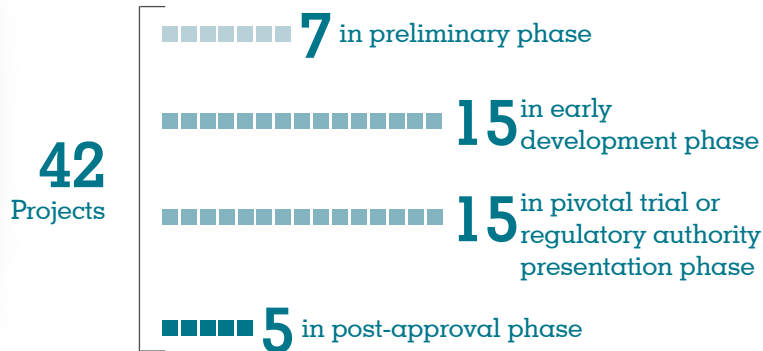
R&D activities follow the Group's strategy and therefore focus on respiratory diseases, neonatology and special care.

In addition to the Foster lifecycle management programme, 2015 was characterised by considerable investment in the development of the triple association, both for the pMDI and DPI formulations. The respiratory pipeline was also further consolidated following new clinical trials for three novel anti-inflammatories and bronchodilators, which have joined the more mature inhalable phosphodiesterase inhibitor.





## Pipeline 2015



In neonatology, the development of new and more efficient Curosurf administration techniques continues, alongside that of the synthetic surfactant, for which two new clinical trials began in 2015. The neonatology pipeline is also developing new programmes concerning bronchopulmonary dysplasia and neonatal brain damage.

Key research and development projects in special care concern Holoclar, a cutting-edge product for corneal regeneration in patients affected by severe burns to the eye, a

gene therapy project for haemophilia B and velmanase alfa for the treatment of alpha mannosidosis, a rare disease involving lysosomal accumulation.

## Industrial operations

The inauguration of the new Curosurf plant in Parma, located within the San Leonardo area, has created the industrial base from which to continue the development of its world-leading product for the treatment of respiratory distress syndrome in preterm neonates, making effective technological improvements to the production cycle. The Blois plant for the production of Foster DPI is now fully operative, and can therefore guarantee the volumes demanded by the market and consolidate the Group's strategy for the development of production centres of excellence.

## The value of teamwork

At organisational level, 2015 brought with it a number of innovations: the creation of the Region Europe, which merges South and North Europe, the complete integration of the IT function across the Group, the setting up of the Global Manufacturing Division, responsible for the global coordination of production activities at the Group's plants and the integration of the procurement activities in Italy. A Centre of Excellence has also been created by the Group Finance, aimed at achieving the uniform development and management of areas relating to Accounting & Reporting. This Centre will be constituted by people from various countries who, whilst continuing to fulfil their responsibilities at their affiliates, will also work together to successfully harmonise the management of these areas for the company as a whole.

## People development

Over the past few years, international development has substantially altered the face of the Group, acknowledging it as a successful global entity among medium-sized pharmaceutical businesses. This is based on a firm belief in the values which have characterised the company since it was created and continue to represent an essential point of reference for its future development. The concept of the centrality of people is one of its



cornerstones and this is why the Group continues to focus its attention on the development of human resources. The People Development and talent database projects are designed to further the growth of Chiesi professionals who are increasingly taking part in international programmes to gain new experiences and opportunities for improvement.

## Priorities for 2016

Commitment to R&D for the development of new products will continue and grow in light of the submission for the Triple association, which is scheduled sometime between October and November. In addition, investment will continue to be made in rare diseases, in particular with the submission of velmanase alfa, which is expected between July and September 2016.

The process of innovation will also involve Business Development, with the aim of finding new opportunities in particular in special care products and maintaining a key focus on the continued international expansion of the Group.

Information technology offers new business development opportunities and the Group has already begun to see its benefits, both for their use within the scope of clinical trials and their potential application in gathering and transmitting data concerning the drug and its use by the patient to the doctor.

On the commercial side, 2016 will continue to be a turbulent year particularly in the emerging countries. Within this panorama, the Group will be required to manage the evolving Turkish market, monitor the complex currency issue in Russia, consolidate its presence in neonatology and the development in the respiratory area in China, support and develop business in Brazil, in order to consolidate its longstanding presence in the largest Latin American market. With regard to the USA, opportunities for growth by means of local business and/or product acquisition will be evaluated.

The main objective is to ensure a sufficient increase in turnover, which will in turn support the growing investment in research and development, required to guarantee the continued innovation at the basis of future growth.

This task will once again be entrusted to the company's people, who through motivation and ideas will contribute to creating a shared future, giving the entire Group a new lease of life and continuing to pursue the ultimate aim of a company whose focus is innovation: the research and development of new drugs which provide patients with therapeutic options able to treat the diseases they are affected by.



# Key events in 2015



● Chiesi Farmaceutici S.p.A. celebrates 80 years



● The Chiesi Foundation celebrates 10 years



● Foster approaches a turnover of 500 million Euro



● Chiesi Nordics is born. It aggregates Denmark, Finland, Norway, and Sweden



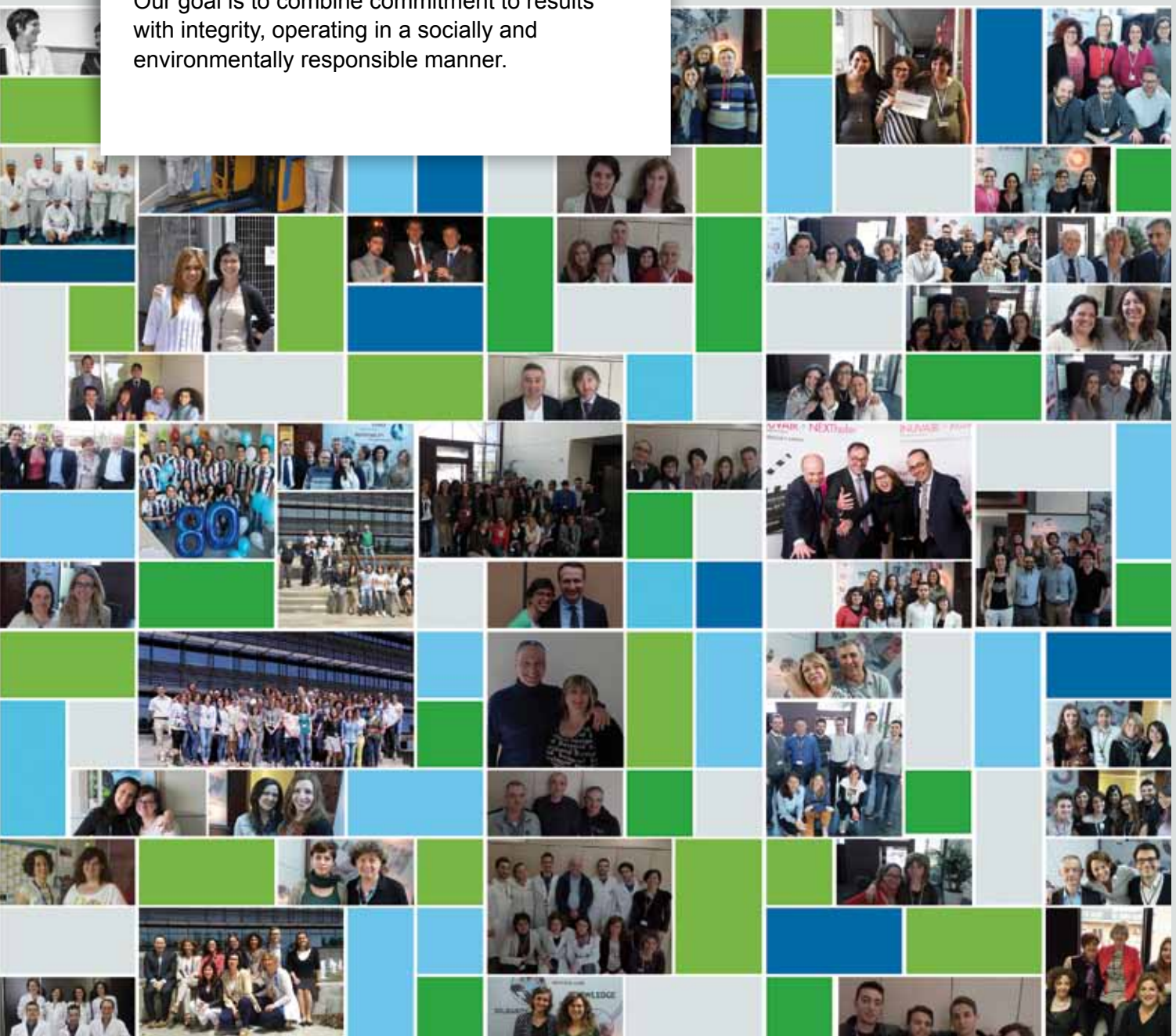
● New organisational model of the Regions, now divided into Europe, Emerging Countries & IMDD, and USA





## Mission

Our aim is to be recognised as a research-focused international Group, able to develop and commercialise innovative pharmaceutical solutions to improve the quality of human life. We want to maintain a high quality entrepreneurial team characterised by self-confidence and a collaborative spirit. Our goal is to combine commitment to results with integrity, operating in a socially and environmentally responsible manner.

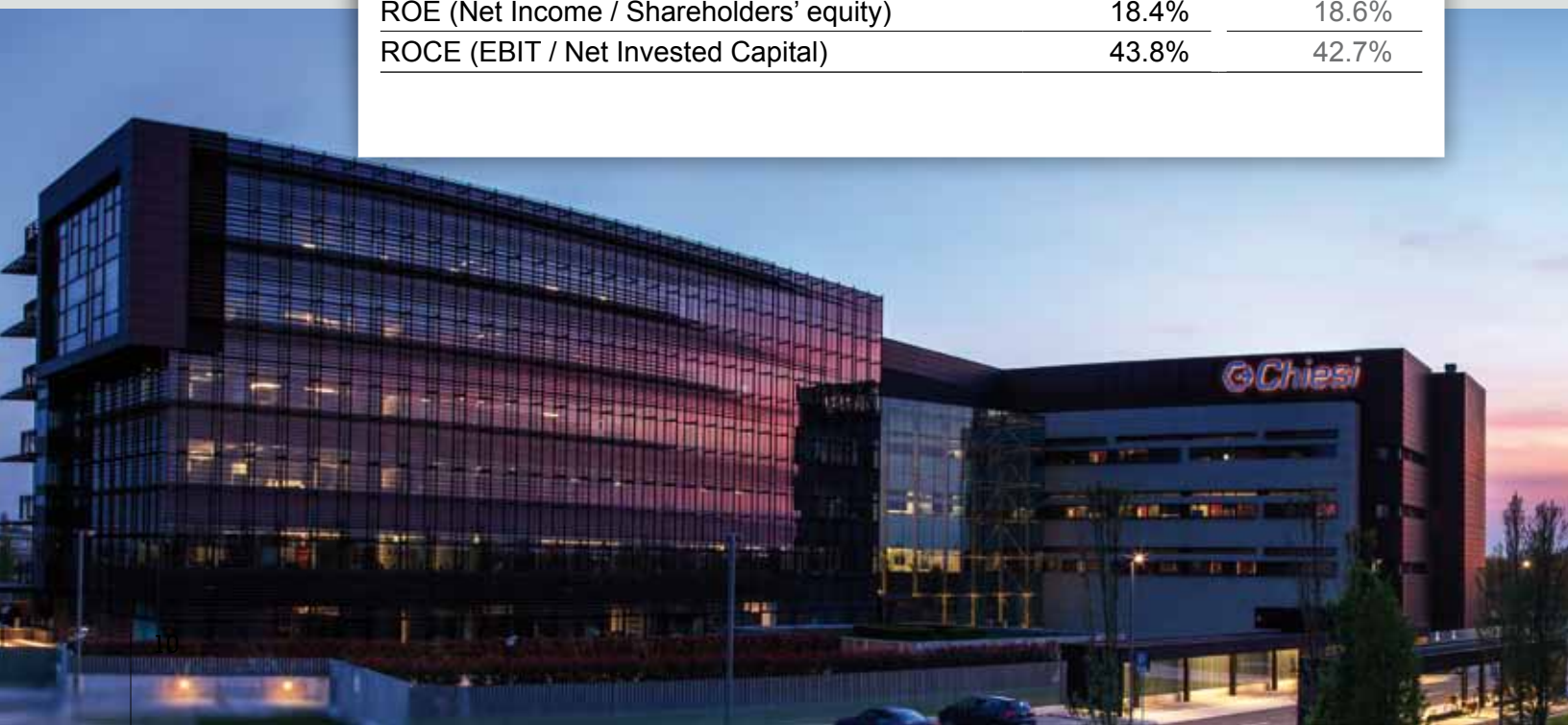


# Key financial results

## 2015 Group Financial Highlights

(Value in Euro/000)

<b>Operating Results</b>	<b>2015</b>	<b>2014</b>
Sales & Revenues	1,467,172	1,341,651
<i>Growth</i>	9.4%	8.4%
EBITDA	407,379	372,385
<i>% on sales and revenues</i>	27.8%	27.8%
Net income	227,668	192,748
<i>% on sales and revenues</i>	15.5%	14.4%
<b>Other Information</b>	<b>2015</b>	<b>2014</b>
R&D costs	301,919	235,540
<i>% on sales and revenues</i>	20.6%	17.6%
Capital Expenditure	68,744	176,350
- Mergers and Acquisitions	1,763	89,428
- Tangible and Intangible assets	67,981	86,922
<i>of which R&amp;D investments</i>	11,517	10,328
Permanent staff	4,252	4,077
Temporary staff	287	325
<b>Ratios</b>	<b>2015</b>	<b>2014</b>
ROE (Net Income / Shareholders' equity)	18.4%	18.6%
ROCE (EBIT / Net Invested Capital)	43.8%	42.7%



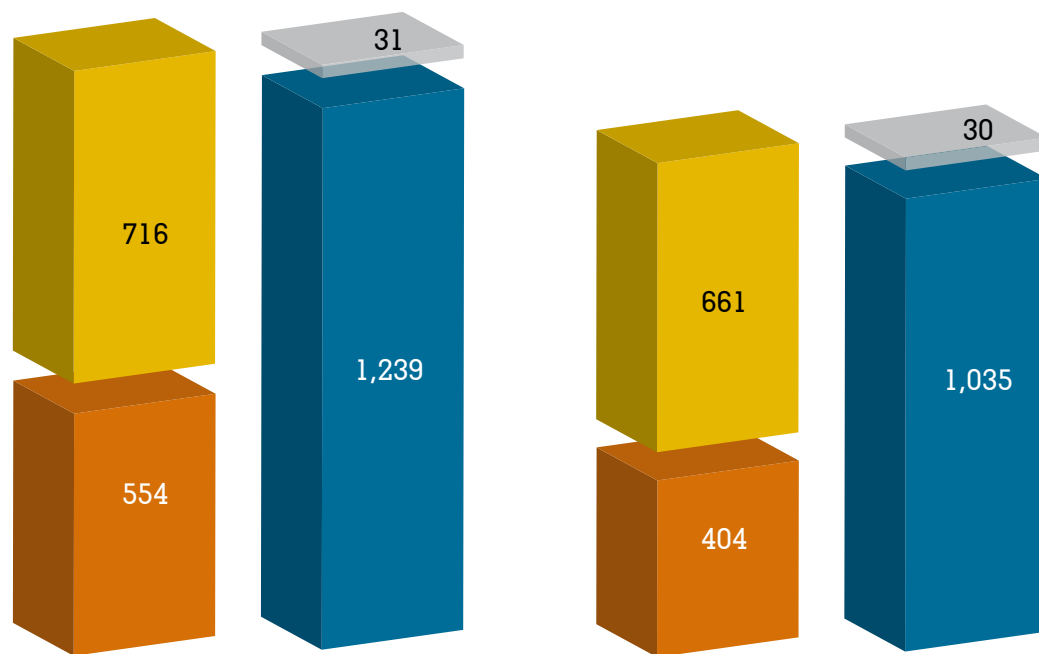


## Group Financial Highlights

(Value in M/Eur)

31<sup>st</sup> December 2015

31<sup>st</sup> December 2014



■ Net Invested Capital  
■ Net Financial Position

■ Reserve Termination & Severance Indemnity  
■ Shareholders' Equity (\*)

(\*) net of owned shares

## Board of Directors

Alberto Chiesi  
 Paolo Chiesi  
 Alessandro Chiesi  
 Andrea Chiesi  
 Maria Paola Chiesi  
 Giacomo Chiesi  
 Ugo Di Francesco  
 Carlo Salvatori

## Board of auditors

Giuseppe Piroli  
 Paolo Alinovi  
 Vincenzo Simonazzi

## Executive Committee

*Chairman*  
 Alberto Chiesi

*Vice-Chairman and  
 R&D Director*  
 Paolo Chiesi

*Chief Executive Officer*  
 Ugo Di Francesco

*R&D Planning and Control  
 Director*  
 Andrea Chiesi

*Strategic Planning Director*  
 Maria Paola Chiesi

*Group Human Resources &  
 Organisation Director*  
 Ugo Bettini

*Corporate Drug Development  
 Director*  
 Mark Parry-Billings

*Global Business Development  
 & Licensing Director*  
 Anton Giorgio Failla

*Strategic Planning Director*  
 Thomas Gauch

*Global Manufacturing Division  
 Director*  
 Giovanni La Grasta

*Corporate Finance Director*  
 Danilo Piroli

*Legal & Corporate Affairs  
 Director*  
 Marco Vecchia

*Corporate Marketing Director*  
 Andrea Bizzi

*Head of Region Europe*  
 Alessandro Chiesi

*Head of Region Emerging  
 Countries & IMDD*  
 Cosimo Pulli

*Head of Region USA*  
 Ken McBean

*Business Development  
 Executive Region US*  
 Giacomo Chiesi



# #02

A woman with long dark hair, wearing a white lab coat and clear safety glasses with red temples, is looking down at something in her hands. The background is a blurred laboratory setting with various pieces of equipment.

## CHIESI 2015

Research & Development Strategy

ANALYSIS - A sphere-shaped project

Global Business Development

Main products

Industrial Operations

ANALYSIS - The new Chiesi Group industrial footprint

Therapeutic Areas

Global Marketing

Corporate Pricing & Market Access

ANALYSIS - The story of the first LPLD patient treated with Glybera

Human Resources

Group Information & Communication Technology

# Research & Development Strategy

## Research, development and innovation remain key priorities

Research & Development (R&D) remains a key priority for Chiesi, with the R&D project pipeline increasingly leveraging novel, proprietary therapeutics that target diseases with high unmet medical need. We want to confirm our track record of high level R&D productivity and deliver effective therapeutic solutions which can differentiate from others in the market. The pipeline continues to focus on the core areas of expertise for the business; namely respiratory medicine and neonatology, with continued expansion of our innovative programmes in special care, where advanced therapeutics in protein, gene and stem cell therapy are being developed.

In addition to the specific R&D milestones summarized in the following sections, 18 new patent filings were made over the year, a key indication of innovative business. Moreover, 25 scientific or clinical papers were published in peer-reviewed journals

and 43 presentations were made at international R&D conferences.

Significant progress has been made at all stages of the pipeline, and also in the geographical expansion of our activities as we seek global registrations for our R&D assets in Europe, the US, the Far East and other key countries.

In 2015 investment in R&D reached approximately €302 million, representing 20.6% of Group revenues and equivalent to a 28.3% increase in spending on the previous year. Spending was balanced effectively between in-house direct costs and judicious out-sourcing to maintain flexibility. Capital investment totalling €12 million was mainly channelled into our state-of-the-art infrastructure and patents. Importantly, more than 70% of Chiesi Group revenues continue to be generated by products developed in the internal R&D pipeline.

## Respiratory: significant progress with established products and the innovative pipeline

**Foster** is a proprietary combination of inhaled steroid and long-acting bronchodilator, formulated for delivery by both a pressurized metered dose inhaler (pMDI) and dry powder inhaler (NEXThaler). Our proprietary technologies ensure an extra-fine aerosol for effective delivery to both large and small airways in the lung: an important differentiating attribute with key clinical and commercial advantages. In 2015, an important milestone was reached with the European approval of the NEXThaler product for COPD. This achievement completed the portfolio of delivery device options and key indications for the medium-strength product.

Two further business-expanding European milestones were achieved for the Foster franchise with

the successful approval of the pMDI and NEXThaler formulated with a higher strength of steroid indicated for patients with severe asthma.

Solid progress was also made with our key respiratory pipeline asset; the **Triple** inhaler. This product candidate combines a steroid and two different bronchodilators in a single inhaler, and is being developed in both pMDI and NEXThaler formulations, targeting the treatment of both COPD and asthma. For the leading product candidate (pMDI for COPD), patient recruitment was completed on track for both pivotal phase 3 trials, representing a key milestone in this clinical programme, which involves more than 8,000 patients. In the pMDI asthma programme, phase 2 trials were success-



fully completed and preparations remain on track for initiation of pivotal trials. For the NEXThaler and broader development programme in the US and Far East, regulatory agency activities were completed in 2015, providing a solid foundation for the global development of this asset, which is the top product in its class.

Our proprietary pipeline of **new molecular entities** comprising anti-inflammatories, bronchodilators and their combinations, also achieved a series of milestones during the year. For our most advanced candidate (a novel inhaled phosphodiesterase in-

hibitor), preparations are on track for an extended phase 2b trial. Three further novel candidates discovered by Chiesi have progressed positively into early development during the year with the aim of entering clinical trials in the near future. These are novel anti-inflammatories (targeting the inhibition of P38 kinase and neutrophil elastase) and a dual bronchodilator (muscarinic antagonist beta agonist or MABA). Moreover, new research initiatives have been initiated to target differentiated small molecule candidates for the idiopathic pulmonary fibrosis and pulmonary arterial hypertension.

## Pipeline



## Neonatology: commitment to life continues

The surfactant replacement therapy **Curosurf**, developed by Chiesi to treat neonatal respiratory distress syndrome (RDS), is a key asset for the business and a foundation for the continued R&D drive to deliver therapeutic solutions for this delicate and under-served patient population. Curosurf is approved for delivery to premature babies via an intratracheal tube; a method which is effective but could be improved using less invasive delivery options. Significant progress was made over the year with the development of a special thin less invasive intratracheal catheter, work to file for European approval is at an advanced stage, and positive progress was made during the year at advisory meetings with the US regulatory agency (FDA). A series of important pre-clinical testing milestones have been achieved in our aerosolized surfactant programme, which is targeting a more advanced and effective non-inva-

sive delivery solution for this life-saving therapeutic. In addition to the animal-derived Curosurf product, Chiesi has continued with the development of a proprietary **synthetic surfactant**, which met a further significant milestone with the positive initiation of a more advanced phase 2 clinical trial within a US Investigational New Drug programme.

Our pipeline in neonatology is expanding beyond the treatment of RDS with programmes targeting indications in bronchopulmonary dysplasia (a lung disease of prematurity with a very high unmet medical need), and neonatal brain injury (another devastating condition for which there are currently no effective pharmacological therapies). A new therapeutic programme was also initiated for neonatal abstinence syndrome, a major issue for newborns particularly in the US.

### 2014 investments



# 302

Total spending in R&D  
(mio €)



equal to

# 20.6%

of revenues invested in R&D



## Special care and rare diseases: effective development of advanced therapeutic platforms

**Holoclar** is a ground-breaking, tissue-engineered advanced therapy medicinal product, which has been developed in partnership with Holostem TA s.r.l. for the treatment of severe corneal injuries due to ocular burns. In early 2015, the product received European Commission approval, making it the first stem-cell product to be approved: a true first for the field and for Chiesi's R&D.

Gene therapy represents another breakthrough approach in therapeutics, and through our partnership with uniQure B.V., Chiesi R&D is co-developing a targeted gene therapy for haemophilia B (AMT-060). This landmark product candidate successfully entered clinical trials in 2015, and initial readouts are imminent.

Velmanase alfa is an enzyme replacement therapy for a rare lysosomal storage disorder called alpha mannosidosis. The pivotal phase 3 trial and long-

term follow-up of all treated patients (up to 4 years) have been completed and clinical data analysis, as well as product development work, progressed during the year to support European filing in the coming year.

A new protein therapeutic has entered the pipeline; a specific proprietary form of **nerve-related growth factor** targeted for topical application for effective wound healing.

Chiesi USA (the Group's US subsidiary) is leading the programmes for two assets in the cardiovascular field. The first leverages an FDA-approved biological product, **Retavase** (recombinant reteplase), which is indicated for the management of acute myocardial infarction. The second development opportunity (**CUSA 081**) further leverages reteplase targeting its use in the indication of clearance of fibrin clots from various types of catheters.

## Chiesi R&D team: a key asset

The R&D team expanded in the year and now totals 560 colleagues (representing a growth of 8.6% on the previous year). Staff are located primarily at the corporate headquarters in Parma (Italy) but also at our sites in Paris (France), Chippenham (UK), Cary (US), Lidingö (Sweden) and Hillerød (Denmark).

Projects are effectively executed by cross-functional global teams in a matrix organization, supported efficiently by functional areas including discovery and non-clinical research, chemistry manufacturing and controls, drug delivery technologies, clinical development, regulatory affairs, pharmacovigilance, intellec-

tual property, quality assurance, project management and leadership, alliance management, and R&D portfolio management.

The expertise and dedication of all of the Chiesi R&D community is an essential part of the continued success of the pipeline and its productivity, which feeds the commercial organization, and more importantly provides effective therapeutic solutions for patients.



### R&D people



560

Qualified people



424

corporate



136

at the affiliates

# A sphere-shaped project

by Stefano Petruzzelli

MD PhD Chief Medical Officer Head,  
Global Clinical Development



An important part of the work done by R&D in 2015 was to pave the way for the use of the triple association with COPD patients.

The department I head [Global Clinical Development – Editor's note] is involved in interfunctional activities which require it to confer with other R&D functions, the headquarters and the affiliates.

When Chiesi launches the triple association it will need to rely on the broadest possible audience of clinicians willing to listen to the message imparting the innovative characteristics of this product. In order to achieve this goal, we have set up a joint programme with some of the affiliates to generate open and constructive discussion with an extensive group of lung specialists

Working with Chiesi Belgium, we have selected a model different from those commonly used to communicate with local clinicians, involving the local medical director, the general management and heads of marketing, and also the staff from Global Clinical Development. Instead of arranging one big single event, we organised a series of small meetings, with no more than ten guests invited to each one.

The meetings followed a shared programme: the Belgian lung specialists were invited to a brief presentation,

followed by an open discussion in which all the participants could take part. The presentation begins with some questions, which open the discussion on the role of steroidal anti-inflammatories in the treatment of COPD. Each question is provided with answers based firmly on biomedical literature and clinical practice.

The decision to open up the discussion to include the origin of the triple association on the premises of the pharmacological approach raised considerable interest and was greatly appreciated by a number of participants attending the meetings. Subsequent to the meetings, the Belgian colleagues once again contacted the doctors who had been invited to ask them what they thought of the event, and their answers indicated that those with initial doubts had begun to reconsider. In my opinion, the most interesting answer was: «The meeting made me think».

Colleagues from both our department and those from the Belgian affiliate took part actively in the project.

The country which will embark on a similar programme, albeit with a slightly different procedure, is Germany. Given the size of the country, the approach made to German lung specialists will entail setting up periodical meetings with more people. Nevertheless, we would like to con-



tinue to develop direct and personal relations with potential users of the triple association as far as possible. The next step will concern France and will adopt the same approach.

As there are still several months to go before the launch of the triple association, these meetings represent an important pre-marketing opportunity, aimed at consolidating the idea that the treatment of COPD can gain a true benefit from the use of steroids.

The three ideas behind this project – peer-to-peer communication, the dissemination of culture, coordination at international level – effectively synthesise the Chiesi Group's approach towards therapeutic innovation.

Our commitment to this aims to create the future success of the triple association and a concrete example of how it is possible to apply innovative methodologies to the launch of our new product.



# Global Business Development

The Global Business Development department focussed its activity on scouting for new opportunities in Respiratory, Neonatology and Special care in line with the Group's strategy to expand and reinforce our presence in these therapeutic areas.

In spite of the significant efforts made to identify and execute acquisitions, no major M&A transactions were completed during the year. This is mostly because of the "overheated" Biotech sector, which over the year led to multiple evaluations and transactions at an economic level difficult to justify from a buyer's perspective.

During the year, Chiesi signed an agreement with Pharmaxis for the distribution of Bronchitol (mannitol, a mucolytic agent) for the treatment of Cystic Fibrosis in some European countries. This agreement follows the one signed with Pharmaxis in 2014, which gave Chiesi the US rights on the product, still in a Phase III clinical stage in that country. A few options concerning research and distribution agreements with companies developing novel early-stage agents for the treatment of serious neonatal pathologies were also signed.

At local level, Chiesi continued to be very active signing a number of agreements for the acquisition and in-licensing, and the divestiture and out-licensing of products.



## Main products

### Foster

A fixed combination of beclomethasone dipropionate (BDP - corticosteroid) and formoterol fumarate (FF - a long-acting  $\beta_2$ -agonist with rapid onset of action) to be taken by inhalation. Foster's key feature is its extra-fine formulation, which guarantees uniform distribution and high lung deposition throughout the entire bronchial tree, including the small airways.

### Foster pMDI

The combination is available as a pMDI (pressurised metered-dose inhaler) in solution. This formulation based on Modulite technology allows one or two inhalations twice daily. Following its launch in Germany in October 2006, Foster is now sold in over 45 countries worldwide, including Russia and China, and in Romania.

Foster can also be administered using the MART (Maintenance And Reliever Therapy) posology. In 2014, Chiesi obtained approval for the treatment of COPD (Chronic Obstructive Pulmonary Disease). The high strength dosage (BDP 200 mcg / FF 6 mcg) was recently added to the original formulation (BDP 100 mcg/ FF 6mcg), as both pMDI and NEXThaler, indicated for the treatment of severe asthma, which is set to be launched in 2016.



Foster



**492 million €**  
turnover

**15.2%**  
world market share (units)

### Foster NEXThaler

In 2013, the new extra-fine powder formulation began commercialization in Germany, the Netherlands, Spain, and Italy. Thanks to the innovative device NEXThaler, it is positioned as the most suitable therapeutic option to satisfy the needs of patients suffering from persistent asthma. In fact, thanks to its extra-fine formulation, triple full-dose feedback system guaranteeing the delivery of the full therapeutic dose and ease of use, Foster NEXThaler is considered a significant step forward in the treatment of respiratory diseases.

Over the last two years, Foster NEXThaler went on to successfully extend its commercial presence through the launches in all the European countries.

Moreover, Chiesi succeeded in gaining approval for the COPD indication for Foster NEXThaler in 2015.

### Atimos (formoterol fumarate)

A pressurised inhalation solution (pMDI) based on Modulite technology and indicated for the long-term symptomatic treatment of asthma and chronic obstructive pulmonary disease (COPD). Thanks to its rapid onset and long-lasting therapeutic action (up to 12 hours), formoterol is considered to be one of the best  $\beta_2$ -agonists currently available on the market.

Atimos ensures optimal distribution of this active ingredient throughout the entire bronchial tree, including the small airways. The drug is sold in all the main European markets and has proven to be well tolerated with respect to other DPI and pMDI formulations.

## Curosurf (poractant alpha)

An animal-derived surfactant for endotracheal administration indicated in the prevention and treatment of neonatal respiratory distress syndrome in premature infants. This syndrome was once the leading cause of neonatal death and it remains a significant contributor to neonatal morbidity. Curosurf is an entirely natural surfactant, mainly composed of polar lipids and proteins. Since its introduction in 1992, Curosurf has been used to treat over 3 million newborns. It is the world's leading surfactant, with a 72% global market share, and is available in over 89 countries worldwide.

Curosurf



over

**3 million**

neonates treated since 1992

present in over

**89**

countries around the world



## Bramitob/Bethkis (tobramycin)

This tobramycin formulation has been developed in a sterile inhalation solution for the treatment of chronic pulmonary infections caused by *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF). The drug is available in mono-dose vials, to be administered twice daily in 28-day therapeutic cycles, alternating with a period of treatment suspension of the same duration. The product showed improved lung function, reduced the need for and length of hospital stays, as well as the number of work and school days lost, and the need for intravenous antibiotics.

Bramitob is Chiesi's first product for cystic fibrosis and is registered and sold in 26 countries, including the USA where the product was launched in November 2013 under the brand name Bethkis.

## Brexin (piroxicam $\beta$ -cyclodextrin)

This is a successful example of the clinical application of "guest-host" technology, which has been awarded the Nobel prize. The host is a starch derivative known as  $\beta$ -cyclodextrin, which solubilises the piroxicam guest, a non-steroidal anti-inflammatory drug, thereby improving its pharmacological properties.

Piroxicam  $\beta$ -cyclodextrin is mainly indicated for the treatment of painful and inflammatory conditions in patients with rheumatic diseases such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

The drug is today sold in Europe, South America, Asia and Africa.

## Clenil (beclomethasone dipropionate)

One of Chiesi's historical products, Clenil has become well established in the market since its launch in Italy in 1979. It is indicated for the treatment of asthma and other inflammatory and allergic conditions, and it comes in a range of formulations (pMDI, DPI, unit-dose vial for nebulisation, nasal shower pMDI).

The pMDI formulation uses Chiesi patented Modulite technology. This has enabled the drug to achieve significant results in European countries, such as Italy and the United Kingdom, where sales and market share record consistent growth.



## Clipper (beclomethasone dipropionate)

It is indicated for the treatment of mild to moderate ulcerative colitis in its active phase. The drug is available in prolonged-release gastro-resistant tablets, to be administered once daily.

The release profile of the product ensures targeted delivery of the active ingredient in the mucosa of the distal ileum and the proximal colon, where the inflammatory process develops.

The drug exerts its anti-inflammatory effect locally and reduces to a minimum the systemic adverse events associated with corticosteroids.

It is currently registered and sold in Italy, Belgium, Spain and the United Kingdom.



## Glybera (alipogene tiparvovec)

A gene therapy product indicated for the treatment of patients affected by Lipoprotein Lipase Deficiency (LPLD). LPLD is an extremely rare metabolic genetic disease (it is estimated to affect 1 individual in 1 million) caused by a mutation in the LPL gene. LPLD patients show severe hypertriglyceridemia and chylomicronemia (accumulation in the blood of chylomicrons, lipoproteins responsible for the transportation of lipids ingested during a meal). Due to chylomicronemia, LPLD patients are at high risk of acute pancreatitis, events that can be fatal and require extended hospitalization, severely impacting the quality of life. Before Glybera's approval, no specific therapy was available; the only therapeutic option for the patients was to

follow an extremely low fat-diet, to which compliance is very difficult to maintain.

Moreover, some patients remained at high risk of pancreatitis attacks despite good compliance with the prescribed diet. The drug is administered via intramuscular injections in the leg muscles: a non-pathogenic viral vector transports a functioning version of the LPL gene into the muscle cells. During clinical development, it has been shown to improve chylomicron metabolism and reduce the occurrence of acute pancreatitis by almost 60% in treated LPLD patients.

Glybera is the first gene therapy product approved in Europe; the marketing authorization granted in 2012 is not only a response to an important medical need, but also a milestone in the world of advanced therapeutics.



*The packaging of Holoclar*

## Holoclar (*Ex vivo* expanded autologous human corneal epithelial cells containing stem cells)

This is the only approved product for the treatment of patients affected by moderate to severe limbal stem cell deficiency (LSCD), due to physical or chemical ocular burns. Holoclar, approved in February 2015, is the first advanced therapy medicinal product based on stem cells.

It is a transparent circular sheet of autologous human corneal epithelial cells. It is created starting from a small limbal biopsy taken from an undamaged area of the patient's eye: the collected cells are expanded in culture to form a sheet containing stem cells that is implanted in the same patient. It is intended for autologous use only.

The limbus is a thin layer of corneal epithelial cells that divides the cornea, a transparent epi-

thelium, from the conjunctiva, a vascularized and opaque epithelium. The limbus contains the pool of stem cells that guarantee periodical corneal regeneration. When the limbus is damaged due to a burn and the pool of stem cells is destroyed, the conjunctiva and the cornea are no longer separated by the important barrier represented by the limbus. The cornea is therefore invaded by the vascularized conjunctiva tissue, which makes it become opaque. This compromises the patient's vision and leads to symptoms such as pain and photophobia.

Holoclar treatment allows both corneal surface repair and stem cell pool restoration. One year after the implantation, treatment was assessed as successful in 72% of treated patients, based on a stable and normal corneal surface, and without or limited invasion of new blood vessels. A reduction in various symptoms was also observed, including pain and photophobia, together with visual acuity improvement.

## Ipersten/Vivace (manidipine)

This latest generation dihydropyridine calcium antagonist is indicated for the treatment of mild to moderate hypertension.

Unlike other traditional calcium antagonists and in addition to its antihypertensive action, manidipine also exerts specific effects aimed at reducing the total cardiovascular risk and improving the quality of life of hypertensive patients.

Today, it is available under different brand names in many countries: Italy, France, Tunisia and Morocco (Ipersten); Brazil (Manivasc); Greece and Germany (Manyper); Spain (Artedil).

Vivace, a fixed combination of manidipine and delapril and ACE-inhibitor fully developed by Chiesi, is indicated for the treatment of hypertensive patients who are not adequately controlled with monotherapy. Vivace combines the therapeutic advantages of manidipine with those attributed to the ACE-inhibitor treatment in terms of efficacy, cardiovascular risk reduction and high tolerability. Vivace is currently commercialized in Spain and Greece and under the brand-name Hipertil in Brazil.

## Velmanase alfa

An enzyme replacement therapy representing the first and only available treatment for patients affected by alpha-mannosidosis, an ultra-rare (1:500,000), genetic disease characterized by the progressive worsening of health

and mental and growth retardation. Patient prognosis is normally poor with death occurring before the 6th decade. Current clinical management is only palliative since there is no approved drug for the management of alpha-mannosidosis.

The only potential treatment for this deficiency is bone marrow transplant, which is considered a “rescue” option with very limited efficacy and significant safety implications to be considered only for patients presenting severe, condition in paediatric age. Velmanase alfa will provide significant improvement in benefits and outcomes for the patient, which means providing greater value for the healthcare system compared to current best practices.



### Peyona (caffeine citrate)

An orphan drug for hospital use only, registered in Europe and countries such as China and Mexico. It was developed for the treatment of apnoea of prematurity. This pathology is mainly due to the incomplete development of the centres in the brain that

regulate respiration. The clinical manifestation of apnoea of prematurity consists of spontaneous pauses in the normal respiratory rhythm, which can lead to dangerous hypoxic episodes in the neonate. Caffeine stimulates the respiratory centres in the central nervous system, increasing the respiratory drive and has been shown to successfully decrease the incidence of apnoeic episodes, reducing the need for respiratory support and the incidence of bronchopulmonary dysplasia. Peyona is marketed in over 20 countries.

### Envarsus (tacrolimus monohydrate)

Available in prolonged-release tablets, this drug is indicated for the prevention and treatment of acute rejection in adult kidney or liver allograft recipients. For more than 20 years, tacrolimus has represented the main pillar in the immunosuppressive regimen, that transplant recipients have to follow for the entire life-

cycle of their grafts. Envarsus is based on the MeltDose technology developed by Veloxis Pharmaceuticals. With the help of this technological platform, Envarsus aims to address the intrinsic flaws of tacrolimus, improving the quality of life for its patients, and allowing more stable plasma levels and a reduced total daily dose needed to achieve the same drug exposure. Thanks to its once-daily dosage, Envarsus simplifies the treatment regimen, helping patients improve their adherence to treatment. It is distributed by Chiesi in all European territories, and in the US by Veloxis Pharmaceuticals. At the present time Envarsus is commercialised throughout most of Europe, including Germany, France, Spain, the UK, Ireland, the Netherlands, Austria, Denmark, Sweden, Norway, the Czech Republic, Hungary and Slovenia.

Several other launches across Europe are planned in 2016, including Poland, Finland, Italy and Belgium.





# Industrial Operations

During 2015, the Corporate Industrial Operations department evolved into the Global Manufacturing Division, centralising the direct management of all the production plants. The new name suggests a wider responsibility, confirmed by the GMD team's remarkable effort to reinforce and extend its industrial capacity. As a result, the Group industrial footprint is now completely renovated to react to the growing needs of the international markets.

## The big project

The GMD targeted major investments to scale up the manufacturing capacity of Curosurf at the Opocrin Plant (API company participated by Chiesi) and the San Leonardo Plant (Parma). These two facilities respectively produce the Curosurf active principle and final product.

Further investments were focused on increasing the production capacity of NEXThaler at the Bepak Plant (UK) and the company plant in Blois (France). Equipment and process validation were also completed at these facilities.

The aluminium-aluminium blister line, located at the San Leonardo Plant, was installed, validated and approved.

These projects share a common technological approach, integrating the concepts of measurability, reproducibility and robustness of processes.







## Other initiatives

A new warehouse for the Parma plant was completed and approved by the authorities. In Brazil, the implementation of SAP was begun without any interruption to business operations. Two new dispensing departments, based on the MES (Manufacturing Execution System) architecture, were finalised in Santana de Parnaíba (Brazil) and Blois (France). Complete track and trace systems were implemented to supply China, Korea and Saudi Arabia, and now fully comply with the traceability requirements (e-pedigree).

## Projects for 2016

The main investment projects for the year include:

- ▶ the installation, validation and approval of the fourth BFS (Blow Fill Seal) line at the San Leonardo department;
- ▶ a further scaling up of NEXThaler Capacity at the Bepak plant (UK);
- ▶ a new liquids line for Rinoclenil in Santana de Parnaíba;
- ▶ the launch of the basic engineering project for a new pMDI department/plant (location to be decided).

# The new Chiesi Group industrial footprint

by Roberto Bugarin  
and Giancarlo Cois

Roberto Bugarin Corporate Engineering  
Director.



There is a precise connection between the Group's strategic vision and the re-design of its industrial dimension, with its new production set-up in Italy and abroad. Growing sales volumes of existing products and new market opportunities require the production plants to be periodically reassessed to ensure they are able to meet this growing demand. Based on the estimates stipulated in the strategic plan, plant saturation is analysed with a view to the future, according to today's concepts of risk analysis and business continuity.

Working on this premise we have taken the opportunity to overhaul some of our production plants. The Curosurf line has been completely overhauled thanks to the new Oporin plant, which produces the active ingredient poractant alfa, and also to the one in San Leonardo, dedicated to the production and packaging of the drug. At the same time, the plant in Blois, dedicated to producing the NEXTHaler technological platform, is now fully operative, and this has increased the production capacity of Foster DPI (inhaled powder). NEXTHaler is also destined for use with future inhalant drugs, beginning with the triple association and phosphodiesterase inhibitor CHF6001.

Furthermore, this device has the characteristics best suited to inno-

vate the product by improving its usability so as to remain competitive through continuous development (Lifecycle management).

The criteria inspiring the creation of these three new plants are based on an industrial approach which ensures processes are reproducible and robust and makes it possible to monitor all the phases of the production cycle.

There are a number of distinctive elements which enabled the GMD team to successfully implement such a complex renovation programme, but the ability to work as a team is the one which stands out from the rest. Complex projects such as these inevitably come up against problems, as happened for example with the Curosurf plant in San Leonardo. Nevertheless, the Chiesi system was able to operate effectively demonstrating its ability to overcome difficulties.

The team met the organisational challenge posed by simultaneously managing three projects, which together are worth more than €60 million. The results of the hard work carried out in 2014, mainly dedicated to setting up the new plants, were seen in 2015, when the team successfully focussed on activities concerning start-up, process validation and preparation for regulatory authority inspections, scheduled for 2016.

Giancarlo Cois  
Corporate Production & Engineering  
Manager



The three projects concerning Curosurf and NEXTHaler are in step with the growth of the company. As a result, the Group can now make

## Future evolution

As a whole, these projects have demonstrated the GMD's ability to manage activities on an international scale, whose strategic premise also entails shifting from a local to international vision for industrial processes. The GMD team is currently working to further consolidate the Group's industrial structure, to guarantee its capacity to respond to future business needs.

The Group's two European plants (Parma and Blois) already meet this fundamental requirement, while the Brazilian plant in Santana de Parnaíba (Brazil) is developing according to the same model and is implementing a modernisation project for the liquid drug production line to meet European standards.

Within the new design, the Parma industrial complex is increasingly tak-

ing on a global physiognomy which develops new technologies to be subsequently extended to the other plants within the Group.

use of a modernised and extended industrial structure to respond to medium and long-term growth plans.

The GMD is therefore in a rapidly evolving phase, which has taken it to an international scale both in respect of its production and level of organisation. This means going beyond the comfort zone and making the most of the new opportunities which internationalisation can offer, integrating the results of experience with the new ideas which often emerge from exchange with colleagues whose experience comes from different contexts. Greater international mobility is one of the keys to success that the GMD will avail itself of to tackle the new technological and organisational challenges continuing to arise as the company develops.

# Therapeutic Areas

## Respiratory diseases

The company is fully committed to the treatment of pulmonary diseases, such as asthma and Chronic Obstructive Pulmonary Disease (COPD). To this end, it has created drug delivery technologies and devices to ensure efficient active ingredient distribution in the lungs.

Foster has been developed in order to provide an innovative treatment; its distinguishing feature is the extra-fine formulation, available both as pressurized Metered Dose Inhaler and Dry Powder Inhaler "NEXThaler".

The formulation is able to release the active ingredient as extra-fine particles, guaranteeing the distribution of the drug throughout the entire bronchial tree, thus ensuring uniform treatment of inflammation and bronchoconstriction both in the central and small airways. In addition to improving asthma treatment, the company is currently engaged in identifying new effective treatments for COPD, a condition which is characterised by a number of therapeutic needs that are as yet unmet. The pipeline consists mainly of projects designed to make significant advances in the treatment of asthma and COPD, thereby continuing to strive towards improving the quality of life of patients affected by these diseases.







## Special care

Chiesi is also focussing its attention on the treatment and care of patients suffering from diseases treated primarily by specialists in the hospital setting, and which can be potentially life threatening. The commitment in this area is considered strategic for the Group's future and more importantly potentially of great social impact. Neonatology has long been a key focus for Chiesi and the company is committed to setting and constantly striving for new standards in Neonatal care.

One of Chiesi's principal treatments is Curosurf, which is the world's leading surfactant trusted for the treatment of neonatal Respiratory Distress Syndrome. In addition, Peyona was developed for the treatment of apnoea of prematurity, and we are exploring new treatments for other conditions that affect the long-term development of preterm infants, such as bronchopulmonary dysplasia.

Another important focus for the company is offering the medical and scientific communities new therapeutic options for the treatment of serious genetic diseases such as cystic fibrosis. The management of

lifelong diseases such as Cystic Fibrosis is extremely difficult for both the patient and the clinical team. Together with the development of Bramitob (launched in USA with the brand name Bethkis) and the acquisition of Hyaneb, important products in the treatment of cystic fibrosis patients, Chiesi has been involved in setting up joint initiatives with physicians and associations to aid adherence and support the management of patients affected by this disease. Since last year, Chiesi has entered into the world of organ transplant with Envarsus, for the prophylaxis and treatment of acute rejection in kidney and liver transplant recipients

## Rare Diseases

Patients with rare diseases typically face a number of issues including difficulty in reaching correct diagnosis, a lack of access to information, scientific knowledge and appropriate quality healthcare.

Chiesi is currently involved in four main areas: Lipoprotein Lipase Deficiency (LPLD), an extremely rare disease with a prevalence of 1:1,000,000; Limbal Stem Cell Deficiency (LSCD), a disease of the cornea caused by loss of limbal stem cells due to chemical and thermal burns; alpha-mannosidosis, a rare, genetic disease characterized by a progressive worsening of physical conditions and mental and growth retardation; haemophilia B, a disease caused by missing or defective factor IX, a clotting protein, and characterized by spontaneous and prolonged bleeding events affecting about 6,000 people in Europe. The current Chiesi Rare Disease franchise has three products in its portfolio: Glybera, Holoclar and velmanase alfa. An additional project for the treatment of haemophilia B is in an early stage of clinical development.

# Global Marketing

## Sponsorships

The Chiesi Group supports many scientific initiatives, actively participating in some of the most important congresses focussed on therapeutic areas of its interest.

### RESPIRATORY AREA

#### ▶ European Respiratory Society (ERS)



The ERS is the leading European professional organization in the respiratory area. Its interests include both basic science and clinical research. Chiesi is one of the main sponsors of the ERS Congress, which each year brings together more than 22,000 respiratory specialists from around the world.

#### ▶ **Sindrome da Distress Respiratorio**

##### *International Workshop on Surfactant Replacement*

The *International Workshop on Surfactant Replacement* can be considered one of the most important events sponsored by Chiesi. It is also commonly known as the “Curosurf Family Meeting” due the limited number of participants, who can attend only by invitation. The first edition of the Curosurf Family meeting was held in 1986, and over the years it has become a worldwide reference point for research in the field of pulmonary surfactants.

#### ▶ **Jens 1<sup>st</sup> Congress Of Joint European Neonatal Societies (Budapest, 16–20 Settembre 2015)**

The jENS congress was one of the most important European events for paediatrics and neonatology in 2015. The congress was made possible thanks to a joint initiative between 4 scientific societies; the ESPR (European Society for Paediatric Research), the ESN (European Society for Neonatology), the UENPS (Union of European Neonatal & Perinatal Societies) and the EFCNI (European Foundation for the care of new born infants). Similarly to the EAPS congress (European Academy of Paediatric Societies), a congress held every two years, Chiesi is one of the major sponsors and has granted its support with an Unrestricted Educational Grant for both for the Bengt Robertson Award and an official session included in the congress programme.

##### *European Society of Neonatologist (ESN) Courses*

Chiesi sponsored this intensive 2-day course that took place just before the jENS congress.



## SOLID ORGAN TRANSPLANT

### ▶ **European Society of Organ Transplantation (ESOT)**

The ESOT is one of the most important international scientific forums whose main goal is to support the active discussion and sharing of clinical experience relating to solid organ transplantation.

The association encourages collaboration between national societies to promote highly scientific communications covering all fields of kidney research including renal physiology, hypertension, chronic kidney disease, transplantation and its related complications.

## RARE DISEASES

### GLYBERA

#### ▶ **EAS 2015 (March 22-25, Glasgow)**

- Silver membership
- Glybera branded booth
- Special lecture: “Severe hypertriglyceridemia: challenges in therapeutic approaches”

Programma creato da EAS con il supporto di Chiesi nella forma di *unrestricted educational grant*

Chair: *M. Averna*. Speaker: *P. Moulin*

- Workshop: FH and severe hyperlipidemias “Gene therapy for Lipoprotein Lipase Deficiency (LPLD): final results of 3 prospective gene therapy clinical studies and 1 retrospective clinical events analysis”

Chair: *P. Moulin*, *A. Rees*. Authors: *S.J. Bernelot-Moens*, *E. S. Stroes*, *A. C. Carpentier*, *D. Brisson*, *M. Andersen*, *C. Meyer*, *M. Bruno*, *D. Gaudet*

- Poster on Geniall publication “First global, longitudinal, pharmaco-epidemiologic, observational registry on GENE therapy In the ManAgement of Lipoprotein Lipase Deficiency (GENIALL)

Presenter: *G. Iotti*; Authors: *E. Steinhagen-Thiessen*, *E. Stroes*, *H. Soran*, *C. Johnson*, *P. Moulin*, *G. Iotti*, *M. Zibellini*, *B. Ossenkoppele*, *M. Dippel*, *M.R. Averna per conto degli Investigators GENIALL*

#### ▶ **ISA 2015 (May 24-26, Amsterdam)**

- Oral presentation: “Gene Therapy for Lipoprotein Lipase Deficiency (LPLD): Learnings From the Clinical Development of Alipogene Tiparvovec, an AAV1 therapy for LPLD”  
Presenter: *S.J. Bernelot-Moens*

- Moderated poster: “Results from the Long-Term Follow-Up of an Open Label Study (CT-AMT-011-01) of Alipogene tiparvovec (AAV1-LPLS447X) for Lipoprotein Lipase Deficiency (LPLD)”  
Presenter: *D. Gaudet*

#### ▶ **EPC 2015 (June 24-26, Toledo)**

- Presentation on LPLD and Glybera’s effect on pancreatitis to a group of pancreatologists from Nordic countries (Society Meeting of the European Study Group on Cystic Pancreatic Tumours, organized by M. Del Chiaro, Karolinska Institutet, Solna, Surgery)

Presenter: *G. Iotti*

- Oral presentation: “Effect of Gene Therapy with Alipogene Tiparovec on the Incidence of Pancreatitis in Patients with Lipoprotein Lipase Deficiency”  
Presenter: C. Meyer

▶ **ISPOR 2015 (November, 7-11 Milano)**

- Poster “Issues affecting quality of life and disease burden in Lipoprotein Lipase Deficiency (LPLD): A first step towards a PRO measure in LPLD”  
Authors: Johnson C., Stroes E.S., Wierzbicki A.S., Moulin P., Bruckert E., Steinhagen-Thiessen E., Gaudet D., Iotti G., Rastelletti I., Ossenkoppele B., Dippel M., Leclerc M., Aversa M.

**HOLOCLAR**

▶ **ISPOR 2015 (May 16-20, Philadelphia)**

- Poster “Cost-effectiveness analysis of ex-vivo expanded autologous human corneal epithelial cells containing stem cells to repair the damaged ocular surface in patients with moderate to severe limbal stem cell deficiency due to ocular burns in the UK”  
Authors: Fordham R, Ciminata G, Madoni A, Magni T, Ardigò D, Pelosi D, Withe M, Sarnelli V, Deltetto I, Domini B

▶ **EuCornea 2015 (September 4-5, Barcellona)**

- Holoclar branded booth
- Sponsored symposium “Pioneering breakthroughs in treating ocular burns”
- Oral presentation: “Holoclar manufacturing process guarantees the release of epithelial sheets containing viable limbal stem cells to maximize clinical outcomes”  
Authors: G. Pellegrini, P. Rama, P. Guatelli, M. De Luca

▶ **EPC 2015 (June 24-26, Toledo)**

- Poster presentation: “The regulatory pathway leading to the European approval of the first medicinal product containing stem cells”  
Authors: G. Milazzo, D. Ardigò, M. Toschi, D. Santoro, G. Pellegrini
- Poster presentation: “HOLOCORE – A prospective, multinational, multicenter, post-marketing authorization approval study for confirming long-term efficacy and safety of Holoclar in moderate/severe limbal stem cell deficiency (LSCD) due to ocular burns”  
Authors: D. Ardigò, F. Cattaneo, S. Matuska, G. Milazzo, M. De Luca, G. Pellegrini, P. Rama
- Poster presentation: “Ex-vivo expanded autologous human corneal epithelium containing stem cells to treat limbal stem cell deficiency (LSCD) due to ocular burns. Retrospective case series that supported the conditional Marketing Authorization of Holoclar in the EU”  
Authors: P. Rama, D. Ardigò, G. Milazzo, S. Matuska, M. Zibellini, M. De Luca, G. Pellegrini

▶ **ISPOR 2015 (7-11 novembre, Milano)**

- Poster “Is regenerative medicine cost-effective? Evidences from the first approved stem cell based product”  
Authors: Fordham R, Ciminata G, Madoni A, Magni T, Sarnelli V.



## Donations

### RESPIRATORY DISTRESS SYNDROME

The Curosurf Team continued to support two projects in Cambodia and Burma in 2015:

- ▶ **Cambogia: Innocent prisoners, "The knot" a No-Profit international association**  
The objective of the project is to assist pregnant women in prison and children who live in prisons with their mothers because they have no better alternative.
- ▶ **Birmaniam: The Health Pediatric Centre, "A Helping Hand For Children" an Italian No-Profit association.**  
The aim of the project is to provide free healthcare for the children of the Moby Parish community, in Myanmar (Burma), an area without hospitals within walking distance (the nearest hospital is several miles away).

## International donations

Chiesi joins some of the most important global initiatives aimed at reducing the impact of the main respiratory diseases on a global scale.

The Chiesi Group supports the following international organisations:

- ▶ **Global INitiative for Asthma (GINA)**  
The Global Initiative for Asthma (GINA) works with healthcare professionals and public health officials around the world to reduce asthma prevalence, morbidity and mortality.
- ▶ **Global Initiative for chronic Obstructive Lung Disease (GOLD)**  
The Global Initiative for chronic Obstructive Lung Disease (GOLD) works with healthcare professionals and public health officials to raise awareness and improve the prevention and treatment of Chronic Obstructive Pulmonary Disease (COPD).



## Patient Organisations

Chiesi Group supports the following international organisations:

- ▶ **RESPIRATORY**  
**European Federation of Allergy and Airway Diseases Patient Association (EFA)**  
The EFA is a European network of patient organisations, prompted by the belief that an international organisation of this kind would be a more effective way of meeting the needs and safeguarding the rights of patients and their carers.



# Corporate Pricing & Market Access

## Business initiatives

The first commercial gene therapy treatment in the western world was a milestone achievement in 2015. Obtaining reimbursement for Advanced Therapy Medicinal Products (such as gene therapies like Glybera, cell therapies and tissue engineering products) has been and will continue to be a challenge; we owe our success to long-term commitment and close cooperation both with other Corporate structures and affiliates, namely Chiesi Germany. The value of the experience we are gaining in supporting access for regenerative medicines goes well beyond their immediate success, as it represents a door open to the future, when the number of therapeutic solutions offering long term remission or even a cure for chronic diseases is expected to increase.

Through the MACH team, we have also started working with the affiliates on the preparation for the Triple launch and P&MA strategy. The Triple combination has already been on the radar for three years, during which our team has been working closely alongside R&D to identify suitable phase III studies design and relevant outcomes with a view to market access.





## Evolution of the organisation

In 2015 a long-term P&MA plan was launched, following a thorough assessment of the primary necessities. The plan has the objective of achieving full potential of the department, expanding geographical scope as well as product coverage, particularly for those under development or evaluation.

We worked on several P&MA support tools to deliver to the affiliates for the launch of new products. The most important deliverables were the Pricing Strategy and Core Value Package for a number of products/projects:

- ▶▶ Triple association;
- ▶▶ Glybera;
- ▶▶ Holoclar;
- ▶▶ Foster lifecycle management;
- ▶▶ Curosurf lifecycle management.

In addition, two posters were presented at the ISPOR congresses (US and Europe) and five MACH meetings were arranged throughout the year. In terms of price approvals, Envarsus almost completed its P&R negotiations and was launched in many European countries; Foster NEXThaler 100/6, Foster 200/6 pMDI, and Foster NEXThaler 200/6.

## Top 3 key objectives and projects for 2016

The main projects in place are the preparation of the Triple Corporate and Local P&MA plans and the economic assessment for velmanase alfa. An Early Access Plan for this latter product, both at a corporate and local level, will also be drawn up this year.

Other key objectives include the treatment of the first commercial patients with Holoclar and the completion of P&R negotiations in the European countries.

# The story of the first LPLD patient treated with Glybera

by Alessandra Madoni

Global Pricing, Reimbursement and Market Access



This is the story that has contributed to changing the future of medicine.

For the first time in the Western world, a gene therapy has been administered in a non-experimental setting as an approved medicinal product; a viral vector has been used to deliver a functional copy of the mutated gene to the patient muscle cells.

Lipoprotein Lipase Deficiency (LPLD) is an extremely rare genetic disease caused by a mutation in the gene that encodes for Lipoprotein Lipase (LPL) and it is estimated to affect 1-2 people in a million.

The story starts with the diagnosis of the patient in her early years, thanks to a blood test showing high levels of blood fat. In fact, the lack of LPL causes the accumulation of the fat-carrying particles, leading to recurrent and acute attacks of pancreatitis.

But what does it mean for a patient to live with LPLD? How does the disease affect daily life?

For this patient, like the majority of patients, having LPLD means constantly living on a low-fat diet. It means strict limitations on a daily basis, affecting family and personal life. It means living every day with the fear of having a potentially life threatening pancreatic attack.

Over the years, doctors prescribed her different medications, mainly consisting of palliative care, but they did not really work as they only targeted the management of symptoms. She was still struggling to live with her condition.

One day, her life changed when her doctor told her about a recently approved product for the treatment of genetically diagnosed LPLD patients suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions...her exact case!

She found out more about Glybera, the first gene therapy licensed in the Western world, which represents the first and only therapy to address the underlying genetic cause of LPLD. For her, the possibility of being treated with the most innovative drug in the modern era represented new hope, and for the society and scientific community in general, remarkable progress in the field of personalised medicine.

From that moment on, a close collaboration began between Chiesi and Prof. Elizabeth Steinhagen-Thiessen, Director of the Interdisciplinary Metabolism Centre at Charitè Hospital University of Berlin, for the treatment of that patient.

In order to make this possible, a



dedicated team was created with different stakeholders. Several people, from production to logistics, from the medical department to marketing, to market access, were actively involved in the preparation of the treatment.

Among the milestones achieved, it is worth mentioning the agreement with the Sick Fund and the patient support program for the follow-up of the patient after Glybera administration. Thanks to a synergic joint initiative and cross-functional teamwork, the patient was treated with the drug on September 8<sup>th</sup> 2015.

The treatment was performed successfully, with a series of intramus-

cular injections to the legs, and no adverse events or adverse reactions were reported. After more than seven months, the patient has a much better quality of life.





This first gene therapy treatment has represented an opportunity in the cure of an extremely rare orphan condition and a milestone in the history of Chiesi.

We are proud of have been able to give a severely ill patient a chance to lead an active and productive life. The company is deeply committed to providing LPLD patients with an effective and safe treatment that targets the root cause of the disease.



# Human Resources

The project which featured most prominently among the activities carried out by Group People Development in 2015 was the definition of a new competence model for the entire Group. This step has also resulted in the Development Centre programme, a series of meetings held at the main affiliates aimed at professionals with the highest levels of responsibility, with which Chiesi's professionals were evaluated in respect of ten competences.

 Thought	<ul style="list-style-type: none"> <li>• Innovating and looking to the future</li> <li>• Demonstrating knowledge of the business</li> <li>• Taking effective decisions</li> </ul>
 Results	<ul style="list-style-type: none"> <li>• Effective planning and execution</li> <li>• Achieving results</li> </ul>
 People	<ul style="list-style-type: none"> <li>• Influencing and inspiring</li> <li>• Building teams and networks</li> <li>• Managing and developing people</li> </ul>
 Self	<ul style="list-style-type: none"> <li>• Gaining credibility and trust</li> <li>• Being resilient and learning from experience</li> </ul>

Furthermore, the Talentia project kicked off, with pre-requisites including the creation of a single information-management system at Group level and the possibility of managing the main processes for the evaluation and development of people. The project became operative at the beginning of 2016 for performance management and people development, both of which are supported by the new Talentia software. This new management system supports managers and HR in using the Management by Objectives system, on which the calculation of the variable remuneration is based, and the performance evaluation process. In addition, it provides invaluable help with people selection and development processes.

International mobility for the Chiesi Group was confirmed as one of the keys to professional development and knowledge sharing. More than 20 people were involved in international mobility projects, which enabled them to carry out their activities in professional contexts different to their own, acquiring cultural elements from the country they were working in and disseminating the best professional practices they had taken with them. The Corporate Departments' strategic plan was formally approved at the beginning of 2016. Its main function is to support the company development plans for the next five-year period by selecting developing high-level professionals who identify with the Group's reference values. The search for outstanding professionals naturally involves looking further towards other markets. This is one of the reasons why there has been a growing focus on Smartworking, which allows people to do part of their work away from the company premises. This project, which was confirmed following a pilot scheme reserved for people living very far from their place of work or those in particular circumstances (e.g.

returning to work after maternity leave), is designed to promote new forms of professional activity to benefit flexibility and the possibility of finding a balance between work commitments and private life. Smartworking forms part of a broader programme of People Care, one of the key components of the company's range of professional opportunities.

Training programmes deserve a separate mention. Training and professional refresher courses have been set up at all the Group's offices, in order to consolidate and enhance people's competences and organisational capabilities. In addition, there is the Chiesi Academy programme, which has a strong international emphasis and is organised into *Development for Executives And Leaders (DEAL)* and Young Talent. The Academy's activities, following a break in 2015, are set to continue in the future.

Among the most outstanding results achieved by Global Human Resources is the Top Employer 2016 acknowledgement, awarded to seven affiliates (Italy, France, Germany, the UK, Poland, Spain and, for the first year, the USA). For the fourth year running, the Chiesi Group was also awarded the Top Employer Europe acknowledgement.

This year's programmes include significant investment in the digitalisation of processes with a particular investment in facilitating relations between people and company via the use of web platforms. Plans have also been made for a new edition of the survey *People Voices*, an essential communications tool between the company and its people which has inspired and resulted in the creation of a number of the projects currently being implemented.



# Group Information & Communication Technology

2015 was a key year for the SAP rollout, now up and running in three more local companies, and for the improvement of most of the Chiesi Group business applications.

## Major achievements in 2015

The implementation and Go Live of SAP was completed in Brazil (June) and in Germany and Spain; these latter both switched on 2016 New Year's day.

The project for the new Electronic Document Management System was started. Initially, the scope of application will be limited to R&D and GMD, but it is expected to be extended to all the departments and local companies of the Group.

The R&D and Production LIMS (Laboratory Information Management System) system has been continuously updated, guaranteeing its capability to be at the cutting edge of technology to answer the increasing business needs.

A new Human Resource Management system was prepared and released to support the processes of Management By Objectives, Performance evaluation and Talent manage-





ment for all Group people. The Human Resources Master Data was released at the same time to support the above-mentioned processes. GICT also completed the feasibility studies for the new corporate pharmacovigilance system and the upgrade of the R&D planning system (Planisware); they will provide the basis for the next implementation projects.

A new Corporate Intranet was designed adopting a Global Approach, i.e. the same look and feel, content organisation and news platform for the whole Group. In 2015 it was implemented for the Corporate Departments and the new intranet template has been used for the Italian Market Company (DFI).

As far as the technological infrastructure is concerned, GICT improved performance and business continuity by adopting a new, up-to-date storage system and implementing an easily accessible network core system in the production environment.

## Strategic Programmes

- ▶ The implementation of SAP in Brazil led to the full alignment of the production models and all the production sites in Italy, France and Brazil are now harmonised;
- ▶ The new EDMS system will host all the documents our affiliates need to share internally and/or with healthcare authorities, following structured workflows that guarantee compliance requirements.



## The evolution of GICT

- ▶▶ At the beginning of 2015, a new ICT organisation went live. The ICT department became Global, with a unique responsibility in terms of strategy definition, budget and projects plan. The guiding principles that inspired us were: integration, standardisation and simplification.
- ▶▶ Keeping this in mind the organisation was projected in a way that guarantees: alignment with the business, independence from adopted technologies, orientation to processes (demand, solution and delivery) and based on international standards (Cobit and Eucip).

## Main objectives for 2016

According to the recently defined Group ICT Strategic Plan, we are carrying out key initiatives to evolve the ICT Applications and Infrastructure target landscape in line with the business priorities and with the Strategic Plan:

- ▶▶ The completion of the first wave of SAP rollout projects with the go-live of the system in the USA, Poland and Austria + CEE;
- ▶▶ The feasibility study of the upgrade of SAP to a new platform which can enable more capacity and a launch pad for new functionalities;
- ▶▶ The implementation and go-live of the new EDMS system, integrated with new functionalities aimed at improving data exchange (eTMF – trial master file) and compliant with the requirements of the regulatory authorities (IDMP – identification of medical products);
- ▶▶ After the feasibility study carried out, the new Pharmacovigilance system will go live at a corporate level and be extended to all the affiliates of Group;
- ▶▶ The new rules for data exchange with the regulatory authorities at EU level (IDMP). This requires a set of new rules and interfaces with the applications currently managing the information in scope;
- ▶▶ The feasibility study for Unified Communication architecture, with the purpose of designing a platform aimed at providing the whole Group with an integrated system for phone, email, instant messaging, presence, video and audio conference.

We are going to continue the improvement of the technological infrastructure in terms of performance, robustness and accessibility with a number of initiatives including the implementation of the network core at the R&D Centre, the new Wi Fi network at the production site, the new Oracle database platform.



# #03

## CHIESI WORLDWIDE

Europe Region

Emerging Countries Region & IMDD

Our Offices

# Europe Region

## Italian Pharmaceutical Division

For the tenth consecutive year the Pharmaceutical Division Italy has performed beyond reference market levels, whilst confirming itself leader within the respiratory sector. The growth rate recorded by IMS (Sell-in figure by value) is +3.4%, net of the dismissal of a licenced product.

The Primary Care Business Unit, which has had a positive year, has gone beyond its sales target of almost €6 million in spite of the lower growth rate compared to the previous year, which was caused by the loss of a key product.

The Special Care Business Unit on the other hand did not reach its budget targets, despite a growth rate of over 21%.

The Sales & Distribution Business Unit also closed the year positively (+5%), yet was likewise unable to achieve its budget target.

The loss of a key product was partially offset by new projects and Line Extension launches, in particular concerning the company's core brands, as well as Business Development activities which have set up new partnerships.

A significant increase in the market shares of Chiesi's main products (Foster, Clenil A, Fluibron A, Rinoclenil) was observed, all of which achieved growth rates beyond those of their reference markets. The year also featured three Line Extension launches: IperClenny, lalulClenny and Fluibron pain and fever.

Business Development activities have contributed to the growth of the Special Care Business Unit, resulting in the launch of two products, Tolep and Sirdalud, completed by the launches of the new formulations of Sirio and Donegal HA. Clody has also improved its performance to go beyond reference market levels this year. Results were also positive for Jumex, whose market share has increased by 20%.

Within the Hospital Business sector, both Curosurf and Ferriprox have confirmed forecasts.

The Clenny A Family, which became a sell-out

market leader in 2015 in the aerosol device market, has continued to grow. Over the course of the year launches were made for the new professional device Clenny A PRO, the complete range of IsoClenny medical devices, the new formulation of Fluibron syrup and Fluibron Dry Cough. Lastly, Brexidol patches have also achieved continued growth (+32.1% by value to sell-out).

Overall the Chiesi OTC portfolio has also grown throughout 2015 (sell-out figure in units YTD November) by around 39% by volumes in a generally stable market (+1.4%).

Over the course of the year a Clenny - lo spazio del respiro visibility project was set up, which was aimed at nominating some specialist respiratory pharmacies as exclusive Chiesi partners.

To further support Fluibron and Brexidol, communication projects aimed at consumers were also created and implemented, meaning that for the first time Chiesi has featured on the radio and television. Investment was concentrated on technology (CRM, e-signatures and the digitalisation and dematerialisation of paper forms), communication (multichannel marketing, websites and direct emailing) and people (projects aimed at people development and those supporting change management). With regard to staffing, the Pharmaceutical Division Italy has remained unchanged with a headcount of 581. 2016 will see the Italian launch of the Foster COPD indication, which will further boost the product, and the development of the Line Extension products. The launch of Clenil Spray 100 is scheduled for the end of 2016.

This year the Special Care Business Unit will extend its portfolio by launching Envarsus, starting up the Line Extension project for products in the Muscular category and consolidating the new business model for Apofin.

The Sales & Distribution Business Unit intends to consolidate the Line Extension project by con-





## Italy



Domestic direct Sales (K€) **267,484**

Variation versus 2014 **-9.7%**



Human resources **581**

Commercial network **436**

tinuing to innovate the product, in addition to various scheduled launches, including Fluibron Effervescent Tablets, the new line of Diesis pressure measurement devices, Ventmax single dose vials for aerosol and in the consumer area, the commercialisation of “New Clenny A Family - Made in Italy”. A number of business projects will kick off during this year for all of the departments; this will include further development in the digital area. The theme of innovation has by now become an in-

trinsic part of company processes and will increasingly form part of Human Resource Management’s commitment to the management of activities aimed at generating new ideas such as the Innovation Team, the Digital Committee and the Innovation Award.

It will be a priority in the field of communication via a new intranet platform and website, in addition to projects dedicated to the company and the city of Parma.

## Chiesi France

The affiliate reported sales revenues of €110.7 million (+7.3% on 2014). As 2015 was the first full year of sales for NEXThaler, the company further consolidated its position in the respiratory area.

Total investments in fixed assets for the line extensions at the facility in Blois reached €24.4 million. The NEXThaler industrial project is ready to go live. Thanks to the development of NEXThaler in 2015, Innovair generated 13.4% growth. The affiliate improved sales force effectiveness, the organisation of sales teams and the commercial model to be on track to start 2016 successfully.

The implementation of the new Special Care team designed to protect Curosurf’s turnover and launch Envarsus successfully was one of the main initiatives for the Special Care BU.

Particular attention was dedicated to the recruitment and training of medical reps and medical scientific liaison managers, KOL mapping and es-

tablishing relationships with new clients and stakeholders, and last but not least, preparing and implementing the launch plan. This strategy ensured that around 100 patients were treated with Envarsus in four months.

Key investments focussed on NEXThaler production at the Blois plant, planned for mid-2016. The company maintained the same headcount both for the headquarters and the sales department; there was significant growth at the Industrial site and the Special Care BU (from 6 to 10 reps + 3 MSL). Major changes were made in Affiliate Management (GM, medical department; Retail BU) and the organisation is now more closely aligned with the Corporate model.

Over the course of 2016, significant growth is expected for Innovair, supported by effective communication, the launch of Innovair NEXThaler for the COPD indication, the reallocation of resources in

2015 and a strong focus on the Impact Plan, a project aimed at increasing the efficacy of rep visits to doctors.

The prelaunch of Innovair 200 is scheduled for the end of the year, while its launch is expected in the first quarter of 2017.

Rinoclenil will demonstrate sustained growth once again of around 30%.

The Special Care BU will focus on recovering growth in Curosurf sales, and ensuring that Envarsus increases its presence on the market.

The company's qualitative objectives include increasing the impact of promotion in hospitals and developing the company's reputation as a reliable partner in the transplant area.



### France



Domestic direct Sales (K€) **110,750**

Variation versus 2014 **7.3%**



Human resources **325**

Commercial network (direct + interim) **173**

### Chiesi Spain

Chiesi Spain's revenues for 2015 exceeded €79.6 million, with an increase of 3.1% on the previous year. This positive result significantly influenced the year's results and the launch of Envarsus improved its presence in the special care area. At the same time, FlogoSport and Produo boosted sales in the OTC market. Teamwork was the main pillar behind the strategies implemented by Chiesi Spain to make people a central focus of the company.

Chiesi Spain worked hard on the development of the beclomethasone and formoterol fixed combination in asthma and COPD. Major activities were also carried out in the transplant and rare disease areas. The Consumer Healthcare Franchise was also further developed, with some line extensions and new products.

Envarsus, a new immunosuppressor for liver and



### Spain



Domestic direct Sales (K€) **79,639**

Variation versus 2014 **3.1%**



Human resources **236**

Commercial network **178**



kidney transplantation, was a challenging launch which took the company into a new therapeutic area. Over the year, 12 new Consumer Healthcare products were put on the market, including those in the Produo and FlogoSport lines. The former is a line of five different probiotic formulations whilst the latter is a specific line for sports people.

The company is preparing the launch for Foster 200/6 and the pre-marketing plan for the triple combination. At the same time, it wants to consolidate the Envarsus launch and make Glybera (an ultra-orphan genetic therapy) and Holoclar (an advanced stem cell therapy for people with chemical or thermal lesions to the eyes) available to patients.

## Chiesi Greece

Chiesi Greece's turnover in 2015 reached €19.7 million, increasing by 14.1%.

The major contributory factor for these results was the launch of 3 new products during the year.

The affiliate's Marketing Division & Field Force were also aligned, which combined with the efforts made by local partners' teams, to achieve results beyond the sales target despite a very challenging market environment.

The most important achievements in 2015 included:

- gaining 35<sup>th</sup> position in the IMS company ranking
- an excellent Foster NEXThaler launch
- achieving a market share of 17.5% for Becloneb (BDP) UDV.

The launches included Foster NEXThaler (September), Manyper 10mg (January), and Becloneb/Beclonpin 400mcg (March), thus helping to establish the product in the local market.

Moreover, the company made investments to increase the visibility of all its products via co-promotional and synergistic activities.



Thanks to a customer service project, the company was able to exploit business opportunities with pharmacies.

Among the main objectives for 2016, Chiesi Greece plans to strengthen the Foster brand against the fixed combination alternatives and improve its staff expertise.

A new entrepreneurial business model approach will also be proposed for all Chiesi Hellas people.



### Greece

	Domestic direct Sales (K€)	<b>19,645</b>
	Variation versus 2014	<b>14.1%</b>
	Human resources	<b>65</b>
	Commercial network	<b>42</b>

## Chiesi Belgium

Chiesi Belgium grew by 8.2% on the previous year with sales totalling €19.8 million.

Sales of Inuvair were up by 11.3% in an increasingly competitive market.

The Belgian affiliate has also expanded, with reps



### Belgium

	Domestic direct Sales (K€)	<b>19,823</b>
	Variation versus 2014	<b>8.2%</b>
	Human resources	<b>41</b>
	Commercial network (direct + interim)	<b>27</b>

working in pairs in each field, and the medical department is now complete (2 new Medical Scientific Liaison team members).

The main objectives for 2016 are to develop and enlarge the portfolio through the launch of Inuvair High Strength and Envarsus.

The head office is to move to larger premises to enable the affiliate to tackle future challenges and in light of the expected evolution of its structures. In September, high strength Foster will be launched and patient access for Glybera and Holoclar will be pursued.

A project linked to “Well-being at work” is also being set up. Investment in training will be significant and will target both technical and soft skills.

Multi-channel marketing initiatives will further increase Chiesi Belgium’s presence in the digital world. In addition, a reinforced Market & Patient Access strategy, structure and approach will be established and a Talent Management programme will be rolled out.

## Chiesi United Kingdom

2015 was a record-breaking year for the UK affiliate. In spite of a PPRS (Pharmaceutical Price Regulation System) rebate to the National Health Service of 10.36% on the total sales achieved, the affiliate was still able to demonstrate overall growth of 12.6% on the previous year, achieving total sales of £136.2 million.

This result enabled Chiesi UK to climb further up the British Pharmaceutical Index to reach the 14<sup>th</sup> Moving Annual Total position (IMS BPI).

The key driver behind this achievement was Fostair, which showed growth in excess of +50% on 2014 after 8 years on the market.

Fostair sales benefitted from a number of line extensions to compliment the COPD indication.

The DPI device Fostair NEXThaler contributed to the overall growth of the product.

Clenil continued to be a key contributor to overall sales with a growing market share and a sales turnover of £47 million.



### United Kingdom

	Domestic direct Sales (K€)	<b>187,538</b>
	Variation versus 2014	<b>25.1%</b>
	Variation versus 2014 in LC	<b>12.6%</b>
	Risorse Umane	<b>210</b>
	Commercial network (direct + interim)	<b>159</b>



Contribution from local products remained significant with growth driven by the key products. The Special Care Business Unit had another successful year with significant contributions from Cursurf, Bramitob and Peyona and the important launches for Envarsus, and Bronchitol. This latter expanded the company's presence within the cystic fibrosis therapeutic area.

Considerable progress was made within the rare disease area which should see important results for the company in the next years.

The progress and growth of the UK affiliate were reflected by the relocation to a new Head Office in Manchester, which effectively doubles the area of working space for this expanding affiliate.

## Chiesi Germany

In 2015, direct domestic sales reached € 118 million. Investments were made in training for the affiliate's teams, including a new structure in the People Development department.

Chiesi Germany has set up a successful marketing programme, which combined with a dedicated sales team contributed to its results.

In January, a new CRM-Tool was launched to support the multi-channel marketing approach. During the year SAP was implemented and went live in January 2016.

In the Primary Care Business Unit the most important achievement was becoming German market leader in terms of prescriptions for Foster. Also, due to an expiring licensing agreement, Chiesi's Forair brand is now the only formoterol pMDI on the German market.

Due to the cost containment measures for Rx drugs at a local level, the company entered into supply contracts (covering more than 50 million patients) to ensure that Foster's success continues. The company also has been able to prevail over other competitors in various tenders for budesonide.



Envarsus, a special care product, has been successfully launched in the German transplant market, a new therapeutic area for the company. Furthermore, a pricing model was successfully negotiated with the German health authorities for a rare disease treatment: the first gene therapy to be approved in the EU.

In October, the affiliate received European marketing authorisation for Foster NEXThaler 100/6.

An In-licensing agreement with Pharmaxis Pharmaceuticals Ltd. has enabled the affiliate to take



### Germany

	Domestic direct Sales (K€)	<b>118,812</b>
	Variation versus 2014	<b>7.3%</b>
	Human resources	<b>209</b>
	Commercial network (direct + interim)	<b>197</b>

over the sales and distribution of Bronchitol, an addition to the cystic fibrosis portfolio in special care. Following the launch of Glybera, the first patient was treated in the autumn in a specialised centre. The year's largest investments were made in Bronchitol and SAP.

Over the year, new organisational structures were established within the Hamburg headquarters, and new structures were also set up for the field-based teams in the Special Care Business Unit.

A key objective for 2016 will be the successful launch of high-strength Foster 200/6 in asthma.

Efforts will be concentrated on generating scientifically sound data for Envarsus, the first MELT-Dose technology based on tacrolimus.

Chiesi Germany is also preparing the launch for Holoclar, the first stem-cell-based therapy for lim-

bal stem cell deficiency caused by lesions to the cornea.  
 The Medical Department is to double the number of field-based Medical Science Liaison representa-

tives in order to address scientific queries from hospital and surgery based doctors more rapidly and effectively, especially in pulmonology and transplantation.

## Chiesi Netherlands



The sales achieved in 2015 by Chiesi Netherlands totalled €34.8 million (13.1% growth).  
 The most important factors contributing to these results were the investments in Foster, now part of GP guidelines and available in the NEXThaler formulation for COPD, Atimos, educational events for the Chiesi College and the Envarsus launch. Significant efforts were also made in building lead-

ership competences and the company's Development Centre has now been opened. In addition, the company enhanced the model of shared values:

- Clean Air for Everybody Foundation;
- Chiesi College (off/on-line CME programmes and services);
- Chiesi Foundation (Fundamental research and scientific talent support).



### The Netherlands

	Domestic direct Sales (K€)	<b>34,828</b>
	Variation versus 2014	<b>13.1%</b>
	Human resources	<b>51</b>
	Commercial network	<b>29</b>

In December Foster reached a 23.1% market share and, as already mentioned, was listed in the Dutch GP guidelines. Moreover, Envarsus and Foster NEXThaler were launched with the COPD indication.

In 2016, investments will focus on Multi Channel Marketing and on the inclusion of Foster in regional and local formularies/protocols. Foster 200/6, Curorsurf 3 ml and Holoclar will also be launched.



For the evolution of the organisation plans have been made for:

- Chiesi Development Centre;
- Talentia;
- Work Council.

## Chiesi Central Eastern Europe

The CEE Group, with its headquarters in Vienna, is the regional structure representing Chiesi in the Central and Eastern European countries (except Poland and Russia) and those within the Commonwealth of Independent States (CIS), providing them with logistics, regulatory, biomedical and economic-financial services. In addition to Chiesi's corporate products in respiratory, rheumatology and neonatology, the regional portfolio has a traditional strength in anesthesiology and intensive care, the rare disease medicine and the treatment of addiction.

### Austria & CEE

	Sales in Austria and CEEC Market (K€)	<b>76,970</b>
	Variation versus 2014	<b>12.0%</b>
	Human resources	<b>196</b>
	Commercial network	<b>99</b>

## Chiesi Austria

Chiesi Austria's portfolio is managed by two business units: Primary Care and Special Care.

The Primary Care Unit focusses on respiratory diseases with its flagship product Foster, now also available as Foster NEXThaler. The product Pro-lastin, which was in-licensed from Grifols (Spain), offers an important treatment for a rare genetic lung disease. Formoterol MDI and a Montelukast generic complete the affiliate's portfolio.

The Special Care Unit has a wide range of products for intensive care, neonatology (Curosurf and Peyona), Bramitob for cystic fibrosis and, since 2015, can also count on Envarsus, a highly promising product.

Chiesi Austria contributes more than 30% to the overall turnover of Chiesi CEE.



## Chiesi Bulgaria

The affiliate was established in 2008. Flamexin, launched at the beginning of 2006, maintains an important position in the antirheumatic area. The affiliate's main products are Curosurf and Foster. For the latter the reimbursement for the COPD indication and the launch of Foster NEXThaler have been further important milestones.



## Chiesi Czech Republic

The respiratory products, especially Foster launched under the brand Combair in 2011, represent the most important and successful part of the affiliate's portfolio. The hospital products Bramitob and Curosurf together with Sufentanil, Midazolam, Fentanyl and a new Bendamustin product make up the special care line.



## Chiesi Romania

In the past, Chiesi Romania succeeded in managing a couple of challenging years in an unfavourable environment for the pharmaceutical industry. The portfolio is mainly based on Curosurf and Flamexin. At the end of 2014 Foster MDI obtained reimbursement, and its launch in early 2015 marks a turnaround for the affiliate.

## Chiesi Slovakia

The local company, operational since 2004, has been consistently successful over the years. Since the launch of Foster, Chiesi Slovakia has enjoyed a high market share compared internationally.

In 2013 the Foster 180-puff formulation was introduced, followed by the launch of Foster NEXThaler, the MART posology and the COPD indication. Curosurf and Bramitob drive the special care area.



### Chiesi Slovenia

This well-established affiliate (operative since 1998) has its most important area of activities in respiratory with Foster and Atimos. Local products such as ReVia and Midazolam Torrex (an anti-addiction drug) also contribute significantly to the results of the company. In 2014, the launch of Foster NEXThaler and the reimbursement of the COPD indication are marking a new era in the respiratory area. 2015 saw Envarsus add a major new opportunity in the special care area.



### Chiesi Hungary

In spite of the difficult pharmaco-economic situation, the affiliate's business has been successfully developed over the years, mainly on the basis of the respiratory franchise (Foster MDI, Atimos), further completed by the launch of the Foster COPD indication and Foster NEXThaler. In 2015 the Foster brand became market leader in Hungary in the ICS/LABA segment. In antirheumatics (Brexin) the affiliate also maintains a strong position, while Curosurf, Bramitob and now Envarsus play a key role in the special care area.

### Chiesi Pharmaceuticals Multi Country Organization

This area, managed by the export division (Multi Country Organization), covers the former Yugoslavian countries, the Baltics and the CIS (excepting Russia and Mongolia). Local partners provide services for registration, marketing and distribution. This region currently represents some 20% of the total revenues for Chiesi CEE, and is considered a major source of dynamic development for the future.

### Chiesi Poland

The Polish affiliate was established at the beginning of 2005, with the main purpose of developing the hospital products (Curosurf, and the anaesthetic portfolio). Bramitob has subsequently been added to the special care product range. Since 2009,

the respiratory products, starting with budesonide and followed by Atimos and Fostex, have boosted the development of the Polish organisation. In 2015 Fostex was the main driver of the company, contributing more than 70% of the total sales and a market share of 30.2%.



In spite of the aggressive generics promotion on the global market in 2015, the Polish affiliate achieved a positive result with a 9.6% growth rate by value, and is one of the fastest growing companies, performing significantly better than the market.

Its next milestone will be Envarsus, which received registration and reimbursement at the end of last year.

The company was certified Top Employer in Europe & Poland for the third time and received the prestigious Forbes Diamond Award for the fastest growing medium companies.



#### Poland

	Domestic direct Sales (K€)	<b>29,852</b>
	Variation versus 2014	<b>9.6%</b>
	Human resources	<b>109</b>
	Commercial network (direct + interim)	<b>77</b>



# Emerging Countries Region & IMDD

## Chiesi Russia

Chiesi Russia demonstrated double-digit growth (+13.5%) in local currency compared to 2014 and maintained profitability despite the turbulent economic situation and the overall decrease in the pharmaceutical market. The most important contributor to these results was a highly motivated team that was determined to reach its targets.

Foster was included in the Essential Drug List and approved by the government at the end of the year. This achievement is the prerequisite for the subsequent inclusion of the drug in Federal reimbursement.

Curosurf maintained its leading position among surfactants with a market share of 95% and a growth of 15.6%.

Vasobral was up by 10% on the previous year despite remaining out of stock for 2 months.

Bramitob reached a market share of 56% thanks to an effective promotional campaign and close cooperation with local charity funds.

The most important investments were in support of the Russian Respiratory Society and the Advisory Board on the importance of the small airways.

Chiesi Russia acquired the Vasobral brand, which is packaged locally. The main objective for 2016 will be to maintain double-digit growth, and ensure Foster is included in the Federal and Regional reimbursement. The office staff moved to new premises at the beginning of the year. The affiliate is set to launch 3 new products: Hyaneb, Sabacomb and Ignisen. The Medical Sales Liaison organisation will be implemented within the Medical department to support its business.



### Russia



Domestic direct Sales (K€)	<b>26,017</b>
Variation versus 2014	<b>-14.6%</b>
Variation versus 2014 in LC	<b>13.5%</b>
Human resources	<b>117</b>
Commercial network (direct + interim)	<b>83</b>



## Chiesi Brazil

2015 was a very challenging year for the Brazilian pharmaceutical market due to a turbulent political scenario, which negatively impacted the economy. Nevertheless, the retail market still achieved double-digit growth. The originator products also performed better than in the previous year, despite facing tough national competition, mostly focusing on the generics.

Compared to 2014, Chiesi Brazil's direct sales decreased by 1.2% in local currency (+3.4% including royalties and sales to local licensees). Retail and private sales grew by +3.8%, pushed by Clenil HFA and Clenil A, reaching a 57.6% market share, as a result of the Farmácia Popular programme.

The Fostair brand also grew by +20.7%, including a full year's sales of Fostair DPI. Public channel sales increased mainly due to Curosurf's outstanding performance of +33.3%.



Two new products, Eflua and Peyona, were launched in order to be more competitive in the OTC market and also enhance the neonatology portfolio, which has already been well-accepted among doctors.

## Brazil



Domestic direct Sales (K€) **54,274**

Variation versus 2014 **-16.4%**



Variation versus 2014 in LC **-1.2%**

Human resources **314**

Commercial network **119**

In June, the affiliate successfully launched the SAP Enterprise Resource Planning (ERP) system.

In 2016, the affiliate will focus on increasing its competitiveness in the Brazilian pharmaceutical market via promotional initiatives and a new Primary Care field force structure, whose primary leverage will be maximising Fostair DPI's full potential.

In addition, plans have been made to modernise the liquid production line at the Santana de Parnaiba site. The main purpose of this project is to align the plant with the corporate industrial processes. This will enable the company to transfer the production of Rinoclenil to Brazil, thus increasing local production volumes.

## Chiesi Mexico

In 2015, total revenues stood at MXN 201.6 million (€11.5 million), representing a growth of 27.6% on the previous year in local currency.

The launch of the primary care respiratory line has made it possible for Chiesi to penetrate the asthma market with Innovair (Foster).

The special and primary care lines made a joint effort to achieve the company's goals.

Government programmes favouring neonatal care have created a positive environment for special care products such as Curosurf and Peyona.

Despite a high level of competition in asthma treatment, Chiesi has been one of the most effective companies in promoting Innovair.

Tenders for respiratory products have allowed the affiliate to extend Clenil's (Axentuo) use in the public healthcare sector.

An educational programme was jointly run with the state and federal government for neonatal nurses, in which more than 600 nurses received training. Peyona has been used in over 200 hospitals to provide therapy for a highly unmet medical need in the country.

Innovair's (Foster) market share in 2015 was 5.1% during its first 12 months of commercialization.

The affiliate ran an asthma awareness campaign, where qualified respiratory therapists performed more than 3,500 spirometry tests.

An all-in-one patient compliance plan was also developed, including spirometry tests, product delivery service and a mobile app that tracks the patient's treatment.

Plans for 2016 include:

- implementing and developing the corporate talent management programme at a local level;
- consolidating respiratory line market penetration;
- obtaining a national tender code granted by the health ministry for Peyona.

Launches are planned for Ribuspir (Budair) and Rinoclenil through a distribution agreement with UCB Mexico. Furthermore, Axentuo's tender business will continue to be developed.



## Mexico



Domestic direct Sales (K€) **11,455**

Variation versus 2014 **28.1%**



Variation versus 2014 in LC **27.6%**

Human resources **31**

Commercial network (direct + interim) **49**

## Chiesi Pakistan



Chiesi Pakistan maintained its traditional dynamism in spite of the conflicting political and law & order situation, generating sales for PKR 1.8 billion (€16.3 million), with a growth rate of 3.3% in local currency.

Brexin remained the top revenue product, with a growth of 20%. Curosurf demonstrated an important growth of 121% on the previous year. Rinoclenil 100 achieved outstanding sales with excellent growth of 153%. Other corporate products such as Foster, Clenil Aerosol, Clenil Compositum Aerosol and Atem Nebulising Solution saw significant growth.

In 2016, Chiesi Pakistan will continue to focus on increasing sales by developing most of its products and launching 3 new drugs (Peyona, CUROSURF 3ml & Clenil Compositum HFA) in the respiratory and neonatology therapeutic areas. The objectives include a higher degree of efficiency and an increasing presence and leadership in the Pakistani



### Pakistan

	Domestic direct Sales (K€)	<b>16,282</b>
	Variation versus 2014	<b>21.6%</b>
	Variation versus 2014 in LC	<b>3.3%</b>
	Human resources	<b>195</b>
	Commercial network	<b>130</b>

pharmaceutical market.

Particular attention will be dedicated to training people in change management, with the aim of promoting greater functional accountability and improving business results.

## Chiesi Turkey

Chiesi Turkey continues to grow and was up 6.7% on the previous year in local currency, despite the termination of the supply & distribution contract for the UCB products. Excluding this negative impact, the company achieved a sales growth of 13%.

The Primary Care BU showed positive results, with a growth of 7% by value and 15% in units with its main products: Foster and Rinoclenil (+26%). Rinoclenil had an extraordinary year, increasing by 25% in units to exceed one million units sold.

The Special Care Business Unit as a whole generated a growth of 20%: Curosurf and Peyona grew by 28% and 73% respectively, and Curosurf's market share reached 87%.



2015 was also a productive year both in terms of marketing projects and sales force effectiveness initiatives. Regarding Foster, the launch of the MART (Maintenance And Reliever Therapy) posology in asthma, the European approval and the Future study in COPD were all key to the growth and success of the product.

Only 7 years since its launch, Curosurf reached a

market of share of over 85% annually, with a peak of 91.7% in December. Despite tough competition,



### Turkey

	Domestic direct Sales (K€)	<b>27,800</b>
	Variation versus 2014	<b>2.6%</b>
	Variation versus 2014 in LC	<b>6.7%</b>
	Human resources	<b>153</b>
	Commercial network	<b>118</b>



Curosurf has been the market driver thanks also to innovative Multi-channel communication marketing projects and strong team spirit. The new neonatology vision has therefore been redefined as “pioneering in neonatology”.

The “Galata” project, aimed at investing in local production and composed of local and global representatives, achieved a complex task thanks to outstanding teamwork to get the greenlight for execution in 2016.

The Chiesi Voices Engagement Survey was once again conducted this year. The results were extremely positive, and scores were doubled in the “Company Image” and “Leadership” categories, with a significant increase in the other areas.

With the launch of the new CLM management sys-

tem, the field force adopted the iPad to present the products to doctors and this instrument is now being increasingly used. The field force has also adopted a “dashboard” to track its KPIs and an improved training tool to encourage professional development and qualitative results.

The company has some ambitious objectives for 2016. In particular, it is looking for and evaluating new Business Development opportunities.

The results of the Chiesi Voices survey have created the premise for new projects, including leadership development, the consolidation of shared culture, media involvement and career programmes.

The Human Resources objective for 2016 is to be awarded the Top Employer certification thanks to these key projects.

## Chiesi China

Group revenues in China exceeded €60 million with 35% growth on 2014. This result was achieved despite the significant market downturn particularly affecting the surfactant area, which only recorded 1% growth. Nevertheless, the whole respiratory market maintained a better growth trend (+11%).

One of the most important factors behind these re-

sults was the expansion of the field force from 66 to 112 reps, with the aim of covering lower tier cities where the market is currently growing faster. With a growing organisation in a huge country like China, the teamwork remains a challenge and this is the reason why the investment was made to strengthen the training department and other supporting functions.

One of the most important achievements was the evolution of Curosurf, whose market share increased by 3.4% to reach 75.8%. Peyona sales achieved €7.4 million, with a positive development of 70% on 2014.

The total headcount was 173 employees, 131 of whom are in the field force. This has been reorganised into 5 regions while the supporting functions at central level were significantly strengthened.

The affiliate’s targets for the current year include reinforcing leadership in neonatology and continued expansion in the respiratory market.

The field force will also continue to expand to improve territorial coverage.

After 2 years of intense activity in market access, a significant development of Foster and Clenil, managed by local joint partners, is expected in 2016.

Plans have also been made to launch Budiair, with the support of another partner.



### China



Primary Sales (K€) **60,322**

Variation versus 2014 **35.1%**



Human resources **173**

Commercial network **131**



## Chiesi USA Inc.

Due to the affiliate's strong team effort in 2015, Chiesi USA achieved its third consecutive year of double-digit growth with revenues in excess of \$247.9 million, representing 16.4% growth on 2014 – a result driven by the team's ability to exceed the targets for four out of five products.

Close collaboration between market access, national accounts and hospital sales teams enabled the affiliate both to retain the existing Cardene business and capitalise on the lack of a Cardene generic. The team also managed to exceed the forecasts for Bethkis even in the face of increased generic competition in the inhaled tobramycin market.

Curosurf's net revenue exceeded \$50 million for the first time and a new market share high was attained. Employee benefits were improved, an internal employer brand was created and a competitive compensation system was set up to drive results and reward top performance. As a result of these initiatives, the affiliate was awarded Top Employer in the US.

The Scientific Affairs department expended significant resources in advancing the technology transfer of Retavase (reteplase recombinant).

Chiesi USA slightly increased its headcount to 146. To simplify the business structure for the R&D de-

partment, all operations have been transferred from Rockville MD to Cary NC. This has allowed the affiliate to capitalise on existing talent and added bench strength to its regulatory and quality teams. The improved organisational structure has allowed pipeline regulatory functions to be integrated and corporate R&D projects to be better supported with a strategic focus on bringing future products to the US market. In addition, the affiliate is investing in the creation of a Medical Science Liaison team to further support its commercialisation efforts.

Key objectives for 2016 include increased revenues, executing the strategic plan, advancing development projects and successfully completing M&A transactions.



The Scientific Affairs department will submit the supplemental Biologics Licensing Application (sBLA) to the FDA for Retavase, and initiate formulation development work for CUSA081.

SAP will also be implemented so that the affiliate's systems can be fully integrated with the Group.

A new sales force automation/CRM system will also be introduced.



### USA Inc.

	Domestic direct Sales (K€)	<b>223,413</b>
	Variation versus 2014	<b>39.4%</b>
	Variation versus 2014 in LC	<b>16.4%</b>
	Human resources	<b>146</b>
	Commercial network	<b>64</b>

## International Markets Development Division

In 2015, the IMDD achieved revenues of over €57.2m, with a growth of 12% in spite of a significant reduction of sales in Europe.

The areas experiencing the biggest evolution have been:

- the Nordics affiliate, as a result of the consolidation and close collaboration of the team, and the development of the Chiesi brand;
- the Middle East, where the support lent by the central functions and area managers to local partners has enabled them to make the most of the opportunities offered by the Chiesi portfolio.

The new IMDD mission and its strategic alignment to the company's plans also played an important part for the Division.

The launch of innovative products in new geographical areas continued: Peyona was launched in South Africa; Foster in Algeria, Indonesia and Kuwait; high strength Foster in Denmark; NEXThaler in Finland and Norway. The team was developed to give maximum support to its partners and the following mission statement was made:

"Grow Chiesi business in all available markets by:

- deploying a proprietary portfolio;
- improving performance in each market and supporting partners in making the most of the opportunities;
- setting up the most appropriate business model".

During the year, further launches are planned for South America and South East Asia.

### IMDD



Sales to distributors (K€)	<b>57,241</b>
Variation versus 2014	<b>11.9%</b>



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# Glossary

**Advanced Therapies:** biologics, based on genetic material, cells and tissues that have been proven effective in the treatment of various diseases. The advanced therapy medicinal products include all new generation therapeutic interventions defined as: gene therapy, cell therapy and tissue therapy.

**Alpha-mannosidosis:** lysosomal storage inherited syndrome, characterised by immune deficiency, facial and skeletal abnormalities, hearing and cognitive impairment. It occurs in about 1 in every 500,000 babies.

**Beclomethasone dipropionate (BDP):** synthetic glucocorticoid with potent anti-inflammatory action. When taken through inhalation, this drug reaches the lungs directly where it exerts its effect. Its low level of absorption in the rest of the body ensures negligible systemic side effects.

**Chronic Obstructive Pulmonary Disease (COPD):** term used to indicate two related lung diseases – chronic bronchitis and emphysema. Both diseases are characterised by chronic and progressive obstruction of the airways, making it difficult to breathe.

**Customer Relationship Management:** the process of managing customer relationships, which is accomplished through four principal activities: the acquisition of new customers, the development of relationships with key customers, the fidelization of key customers, the transformation of existing customers into ambassadors of the quality characterizing the products and/or services of the company. Although the processes of CRM are often supported by IT systems, these latter have a purely instrumental function and by no

means can replace the relational system of the company .

**Cystic Fibrosis (CF):** chronic hereditary disease of the lungs and the digestive system, which currently affects roughly 70,000 people worldwide. A mutated gene creates a protein that causes production of a thick viscous mucus that accumulates and renders breathing difficult. This in turn makes it easier for secretions to build up and consequently promotes the development of dangerous infections. In the digestive system the mucus tends to block ducts in the pancreas and prevents digestive enzymes from working in the intestines, which leads to malabsorption of food and stunted growth.

**Dry Powder Inhaler (DPI):** a device for administering drugs in the treatment or control of respiratory diseases and conditions.

**Generally Accepted Accounting Principles (GAAP):** term used to refer to the standard framework of guidelines for financial accounting used in any given jurisdiction; generally known as Accounting Standards. GAAP includes the standards, conventions, and rules accountants follow in recording and summarizing transactions, and in the preparation of financial statements.

**Hydrofluoroalkanes (HFA):** propellants used in some inhalers for the management of asthma. They do not damage the ozone layer. A propellant is a gas which facilitates the diffusion of an inhalant drug in the lungs.

**Lipoprotein lipase deficiency:** very rare inherited disease due to which patients cannot metabolize the fats in the blood, which causes inflammation of the pan-

creas (pancreatitis), a condition extremely serious, painful and potentially deadly.

**Long-acting Beta-agonists (LABA):** drugs which open peripheral and central airways and keep them unobstructed by relaxing bronchial smooth muscle. LABAs are often administered with steroids in inhalation form as a long-term bronchodilation treatment for patients with moderate to severe asthma or other chronic lung diseases.

**Manufacturing Execution Systems (MES):** solutions that support the primary production processes in a production plant. These applications close the gap between ERP systems and production equipment control or SCADA (Supervisory Control And Data Acquisition) applications. MES applications have become essential to support both real-time production control as well as the data collection and reporting (“manufacturing intelligence”) necessary to improve production performance.

**Muscarinic agonists:** defined as direct parasympathomimetics. Among the main pharmacological effects, they have the potential to cause contraction of the smooth muscle of the bronchi.

**Muscarinic antagonists:** defined as parasympatholytic. Among the main pharmacological effects, they have the potential to cause relaxation of bronchial smooth muscle.

**Piroxicam  $\beta$ -cyclodextrin (PBC):** a successful example of “host-guest” technology, whereby the host, a starch derivative known as  $\beta$ -cyclodextrin, solubilises the guest, an anti-inflammatory drug known as piroxicam, thus enhancing the pharmacological properties of its active ingredient.

**Pressurised Metered-Dose Inhalers (pMDI):** a device which ensures that a specific quantity of drug is delivered to the lungs. Widely used by the Chiesi Group for its products, it is commonly employed in the treatment of asthma, Chronic Obstructive Pulmonary Disease (COPD), and other respiratory conditions.

**Pulmonary dysplasia:** lung disease that usually starts as a RDS and then tends to become chronic and determine the need to assist the infant in terms of breathing

**Respiratory Distress Syndrome (RDS):** disease typically affecting premature neonates caused by insufficient production of endogenous surfactant and immature lungs. The condition may also be due to a genetic problem linked to the production of proteins associated with the surfactant. RDS affects 1% of neonates and is the main cause of mortality in premature infants.

**Unit-Dose Vials (UDV):** non-reusable sterile containers holding a single dose of drug. Pharmaceutical products packaged in vial or mono-dose bottles are easily recognisable and simple to use.

**Ulcerative Colitis (UC):** inflammatory bowel disease (IBD) which causes lesions known as ulcers to develop in the lining of the colon and rectum. Ulcers form where the inflammatory process destroys the cells which normally line the colon, causing in bleeding and pus. The inflammation may also result in frequent bowel movements, and therefore diarrhoea.

**Spacer:** a type of add-on device used by asthmatics to increase the efficacy of the inhaler.

# Chiesi Farmaceutici S.p.A.

## Proprietary Brands

Atem	Clody	Innovair
Atimos	Combair	Inuvair
Becloneb	Curosurf	Ipten
Beclospin	Diesis	Manyper
Bethkis	Donegal	Modulite
Bramitob	Flamexin	NEXThaler
Brexidol	Fluibron	Peyona
Brexin	Forair	Sabacomb
Budair	Fostair	Sirio
Clenil	Foster	Ribuspir
Clenil Compositum	Fostex	Rinoclenil
Clenny	Holoclar	Ventmax
Clipper	Hyaneb	Vivace



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