# ANNUAL REPORT 2013

ENGLISH

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# RESULTS & OUTLOOK

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EXECUTIVE COMMITTEE

# The Chairmen's message

Alberto Chiesi
*Chairman*

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

The initiatives set up in 2013 made significant and irreversible changes to the structure of the Group, laying firm foundations for its future development both in the therapeutic areas in which it has established its leadership, such as that of respiratory diseases, neonatology and some rare diseases, and in cutting-edge sectors such as regenerative medicine, recombinant enzymes, gene therapy and the prevention of organ transplant rejection. This broad and far-sighted commitment combines with an excellent sales performance, up by 11.8% on the previous year, and the Group's best-ever economic result.

These results are even more commendable as they were achieved in a worldwide pharmaceutical market which according to the IMS recorded a lower rate of growth in 2013: +0.4%. The five largest markets in Europe showed a slightly positive trend (+2.5%), whereas some Eastern European markets experienced faster and more complex growth rates. In 2013 the global market in Italy grew by +2.6%, driven exclusively by the hospital sector. In the USA, which remains the largest market in the world, retail drug sales continue to drop slightly, whilst the market for products dedicated to special care continues to increase.
In the emerging countries, and in Brazil and Russia in particular, growth continues albeit at a slower rate, whilst China it is progressing rapidly (+16.1%).[1]
In this somewhat difficult scenario, the Group's development policy resulted in an expenditure of € 168 million in Research and Development on the one hand, and increased investment in acquisitions of firms, new products and new development projects, in industrial plants and research equipment on the other, for a total of more than €118 million. This is confirmation of a desire to develop new special care therapies and improve the quality of production and research. Global presence, innovation and focus on the therapeutic areas of greatest interest continue to represent the guidelines for the future growth. For the next few years in particular, the Group's main priority will be to continue safeguarding the respiratory market, in view of the growing attention of competitors towards this therapeutic area and the risks associated with the possibility of the arrival of generics.

2013 was also the year in which Chiesi became one of the world's top 50 innovative pharmaceutical companies and was characterised by a number of key events: the Nexthaler launch in Germany,

*1 IMS MIDAS - MAT Q3 2013.*

Spain, the Netherlands and Italy, the kick-off of the registration procedure for Envarsus (prevention of kidney transplant rejection) and the commercialisation of Foster and Clenil in China, and the completion of the acquisition of Cornerstone Therapeutics, which opens up significant development prospects in the USA.

A separate mention must be made of the acquisition of the biopharmaceutical firm Zymenex and its product Lamazym, indicated for the treatment of alpha-mannosidosis, the acquisition and co-development of the gene therapy Glybera, indicated for the treatment of Lipoprotein Lipase Deficiency (LPLD) and the new registration procedure for Holoclar (corneal regeneration following lesions from thermal or chemical burning) in the regenerative medicine sector. The Group's presence in these therapeutic areas contributes to the development of new models of medicine, which today are already able provide treatment options for patients who as yet have no available therapy for their diseases and which promise important developments in the future.

In order to respond to the challenges posed by the entry into these new sectors, the Group's Research and Development Department is adopting a new governance system able to manage this phase, which will entail a significant increase in the number of projects and considerably higher levels of funding. As a result, the conditions needed to continue supporting growth will be created, using the innovation provided by new research activities as leverage.
In accordance with its values and identity, the Group is also dedicating greater efforts to all of the social responsibility issues: environmental protection, safety at work, people care projects, economic support for research and medical community training programmes, liberalities for projects of proven social utility. The Chiesi Foundation provides an invaluable contribution to this area through its funding activities for research and its humanitarian initiatives in some of the poorest countries.

Our appreciation goes to our managers and co-workers: it is thanks to the professionalism, spirit of initiative and passion with which they carry out their work day by day if the Group as a whole continues to grow and strive for constant improvement beyond purely economic values. These people's determination has promoted sustainable growth in a climate characterised by team effort, a desire to improve and full respect for values – which are of fundamental importance for us – , the integrity of personal commitment and enhancement of the contribution which each of us can make to the process of building the present and above all the future.

# The CEO's analyses

Ugo Di Francesco
*Chief Executive Officer*

2013 was an important and extremely positive year for the Chiesi Group, which achieved sales for € 1,237 million, up by 11.8% on the previous year. This result, 70% of which was due to internal growth and only the remaining 30% thanks to the albeit significant acquisitions made, represents a source of satisfaction for the company as it has kept to its long-term development programme. The sales trend in Italy, which shows a 5.6% growth rate in a flat market, was overtaken by that of international sales, now into double figures in most countries: the total amount for these latter sales therefore currently represents 75% of the Group's turnover.
This achievement is yet more positive if we consider that the three most important products – Foster, Curosurf and Clenil – have made progress in nearly all their markets. The market shares of Foster, Nexthaler and related brands have increased significantly everywhere, with overall unit sales of 12.5 million and a turnover of € 340 million, up by 22% compared to 2012; in the Netherlands, Poland, the Czech Republic and Slovenia the increase compared to 2012 is more than 20%. Foster, with Nexthaler and related brands, continues to be the main driver behind the company's development, and remains the best-selling Italian drug worldwide in the last decade, in the same way as Curosurf is in its therapeutic area.
The Nexthaler dry-powder inhaler offers optimum lung penetration due to the fine particle fraction of its active ingredients and is simple and easy to use: this makes it a product of undisputed quality. Most of the investments made in production were therefore intended to the increase production capacities of this innovative device, which will be launched in eight countries this year (in Europe and Brazil) and in two further countries next year. This intense marketing programme covering several continents, which follows that of Foster aerosol, is confirmation that all future products will be subject to global development programmes. The contribution to our growth made by R&D in 2013 was also marked by a series of successes:

- the second-wave European approval of Nexthaler;
- the completion of the registration procedure for Bethkis (sterile tobramycin solution) in the USA, which has enabled Cornerstone Therapeutics to make its launch;
- the European regulatory filing of Holoclar for corneal reconstruction following lesions caused by thermal or chemical burning;
- the filing of the COPD indication for Foster;
- the continuation of the Foster high-dosage clinical trials;
- the successful continuation of the development of the phosphodiesterase-4 inhibitor via inhalation and that of the synthetic surfactant.

The phase 3 trials for the clinical development of the triple combination for COPD and asthma, which began at the end of 2013, are destined to feature prominently in 2014 and the next few years until the launch of the product because of their scope. These numerous trials mean that proactive and effective discussions are already taking place with the EMA and the other regulatory agencies; furthermore, they will require the internal governance and relations with external R&D partners to be organised simply and effectively.
As already mentioned in the Chairmen's Message, the Group has acquired new

products and projects in special care therapeutic areas of particular interest. Of particular note is the agreement with the Dutch company uniQure for the commercialisation in Europe and selected countries of Glybera (alipogene tiparvovec), the first gene therapy approved in the western countries and indicated for the treatment of lipoprotein lipase deficiency (LPLD); the agreement includes the co-development of a therapy for haemophilia B.

The acquisition of the Danish biopharmaceutical company Zymenex Holding A/S, which specialises in Enzyme Replacement Therapy (ERT), has resulted in the Hillerød (DK) and Lidingö (SV) laboratories being integrated into the Chiesi research team. This will save a significant amount of time during the necessary process of acquiring specific scientific know-how in HRT, a sector which the Group entered with the intention of remaining. The acquisition includes Lamazym, a recombinant enzyme in phase 3 with an indication for alpha-mannosidosis, a genetic disease which causes the progressive deterioration of the central nervous system, and two compounds for other ultra-rare indications in pre-clinical development.

In the prevention of organ transplant rejection, approval for Envarsus (LCP-Tacro) from the EMA is expected in September. The Group intends to provide additional commitment and all the necessary resources for a long-term development programme.

Foster and Clenil have been launched in China with extremely promising growth prospects in the medium-term, bolstered by the excellent opportunities offered by the local market. The industrial operations have been able to guarantee the production of both the old and new products to meet market demands, and the progress expected as a result of the new lines in Parma, Blois and Santana de Parnaìba, thus creating the conditions to keep up with the development of the business.

The new SAP management system went live according to schedule and the roll-out programmes in France and the UK will be complete by the end of 2014. The other affiliates will follow suit in order to standardise the management of information and data handling.

From the point of view of commercial organisation, the regionalisation process has been consolidated, thus reinforcing sales management in the various countries and reducing the distance between the affiliates and the headquarter functions. The profound changes affecting the Group require a considerable effort from the Human Resources department where the selection of new professional figures, the professional and managerial development of young managers and training activities are concerned. Communications, whether externally with stakeholders or internally between the various functions, are also defining new professional standards to suit the growing complexity of the business.

For the current year, the company intends to continue serving patients worldwide, keeping Chiesi's entrepreneurial spirit, values and story alive. This year is also characterised by the process of integrating Cornerstone Therapeutics, which will shortly be officially named Chiesi USA. Investments in general, and those made in R&D in particular, will increase in line with the growth objectives set. The results achieved in 2013 and the cohesion, commitment and responsibility constantly demonstrated by all of the company's people are the best premises on which to aspire to equally outstanding results in 2014.

# The most important events in 2013

Acquisition of **Cornerstone Therapeutics**

Chiesi enters the top **50** companies worldwide

**2** acquisitions of companies / innovative products (Glybera, Zymenex)

**2** respiratory products launched **launched in China** (Foster, Clenil)

**1** product for cystic fibrosis launched **in the US** (Bethkis)

**Foster Nexthaler launched in 4 countries**

**2** registration procedures for innovative products (Envarsus, Holoclar)

# Our 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

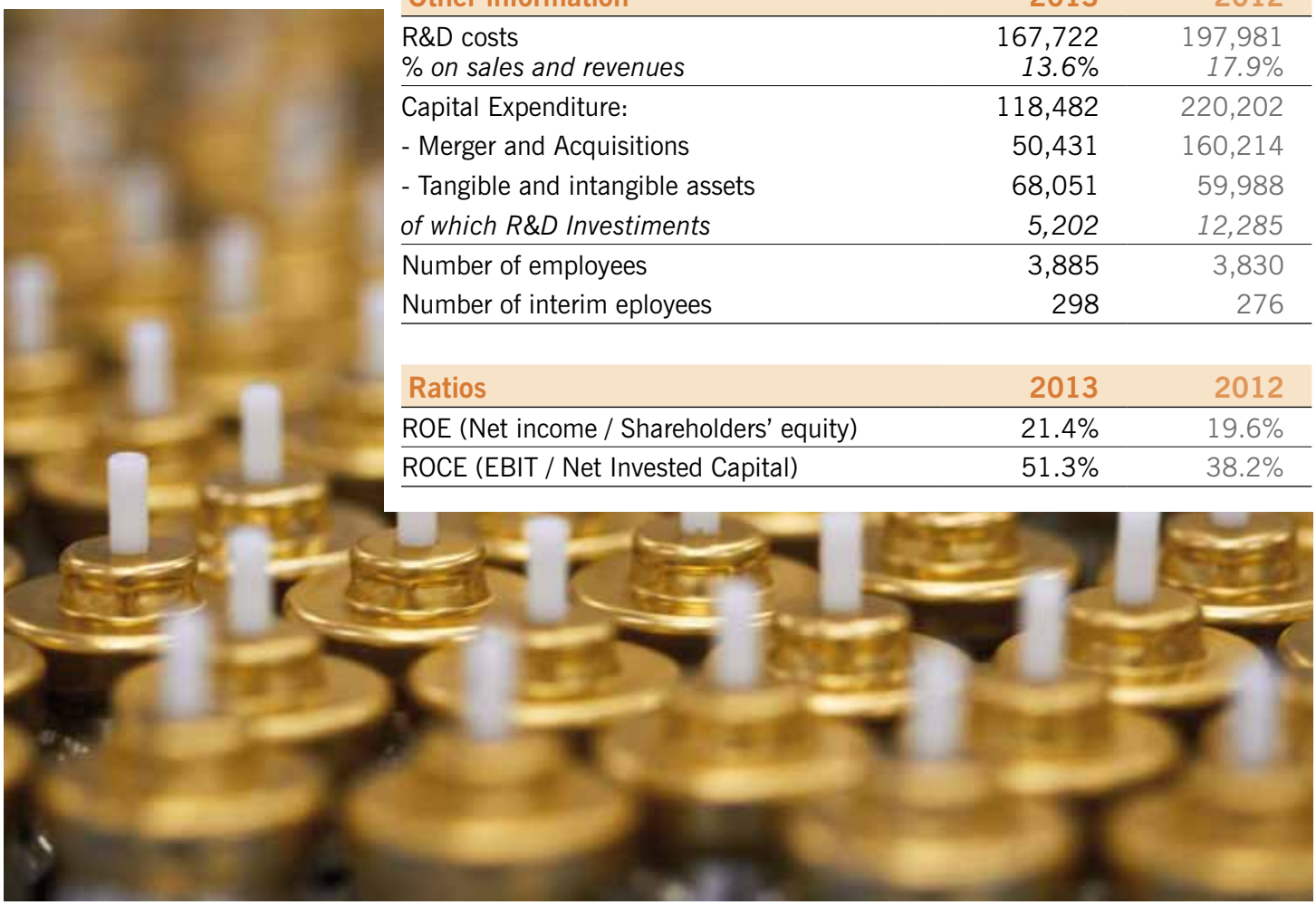
## 2013 Group Financial Highlights

**(Value in Eur/000)**

| Operating Results | 2013 | 2012 |
|---|---|---|
| Sales & Revenue | 1,237,283 | 1,106,808 |
| *Growth* | *11.8%* | *4.7%* |
| EBITDA | 360,426 | 247,120 |
| *% on sales and revenues* | *29.1%* | *22.3%* |
| EBIT | 296,576 | 182,355 |
| *% on sales and revenues* | *24.0%* | *16.5%* |
| Net Income | 183,752 | 130,971 |
| *% on sales and revenues* | *14.9%* | *11.8%* |

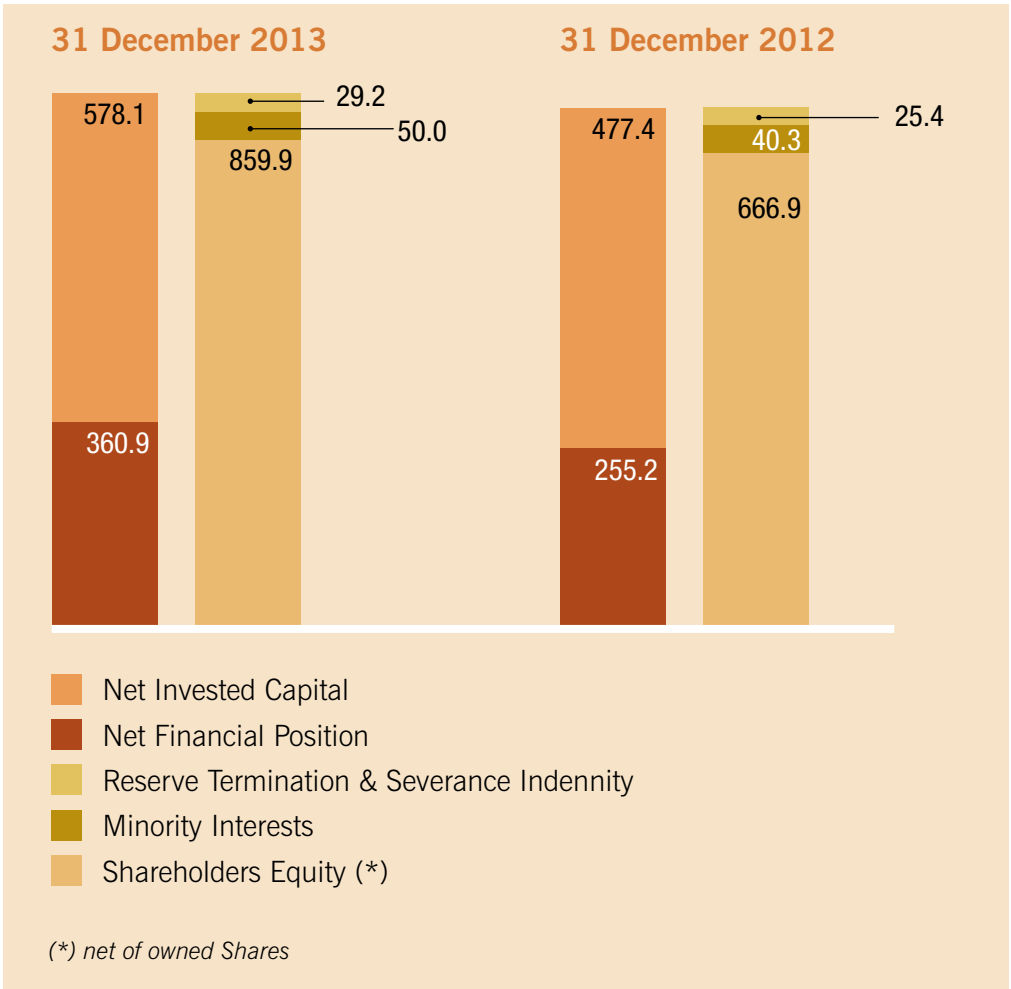
| Other information | 2013 | 2012 |
|---|---|---|
| R&D costs | 167,722 | 197,981 |
| *% on sales and revenues* | *13.6%* | *17.9%* |
| Capital Expenditure: | 118,482 | 220,202 |
| - Merger and Acquisitions | 50,431 | 160,214 |
| - Tangible and intangible assets | 68,051 | 59,988 |
| *of which R&D Investiments* | *5,202* | *12,285* |
| Number of employees | 3,885 | 3,830 |
| Number of interim eployees | 298 | 276 |

| Ratios | 2013 | 2012 |
|---|---|---|
| ROE (Net income / Shareholders' equity) | 21.4% | 19.6% |
| ROCE (EBIT / Net Invested Capital) | 51.3% | 38.2% |



## Balance Sheet Structure

**(Value in M/Eur)**




*(*) 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

*Corporate HR & Organisation Director*
Ugo Bettini

*Corporate Drug Development Director*
Mark Parry-Billings

*Corporate Business Development Director*
Anton Giorgio Failla

*Corporate Industrial Operations Director*
Giovanni La Grasta

*Corporate Finance & Control Director*
Danilo Piroli

*Legal & Corporate Affairs Director*
Marco Vecchia

*Corporate Marketing Director*
Giuseppe Chiericatti

*Head of Region South Europe*
Alessandro Chiesi

*Head of Region North & Central Europe*
Thomas Gauch

*Head of Region Emerging Countries*
Cosimo Pulli

*Head of Region US*
Ken McBean

# CHIESI 2013

RESEARCH & DEVELOPMENT STRATEGY

BUSINESS DEVELOPMENT & STRATEGIC ALLIANCES

MAIN PRODUCTS

INDUSTRIAL OPERATIONS

THERAPEUTIC AREAS

GLOBAL MARKETING

HUMAN RESOURCES

INFORMATION & COMUNICATION TECHNOLOGY

# Research & Development Strategy

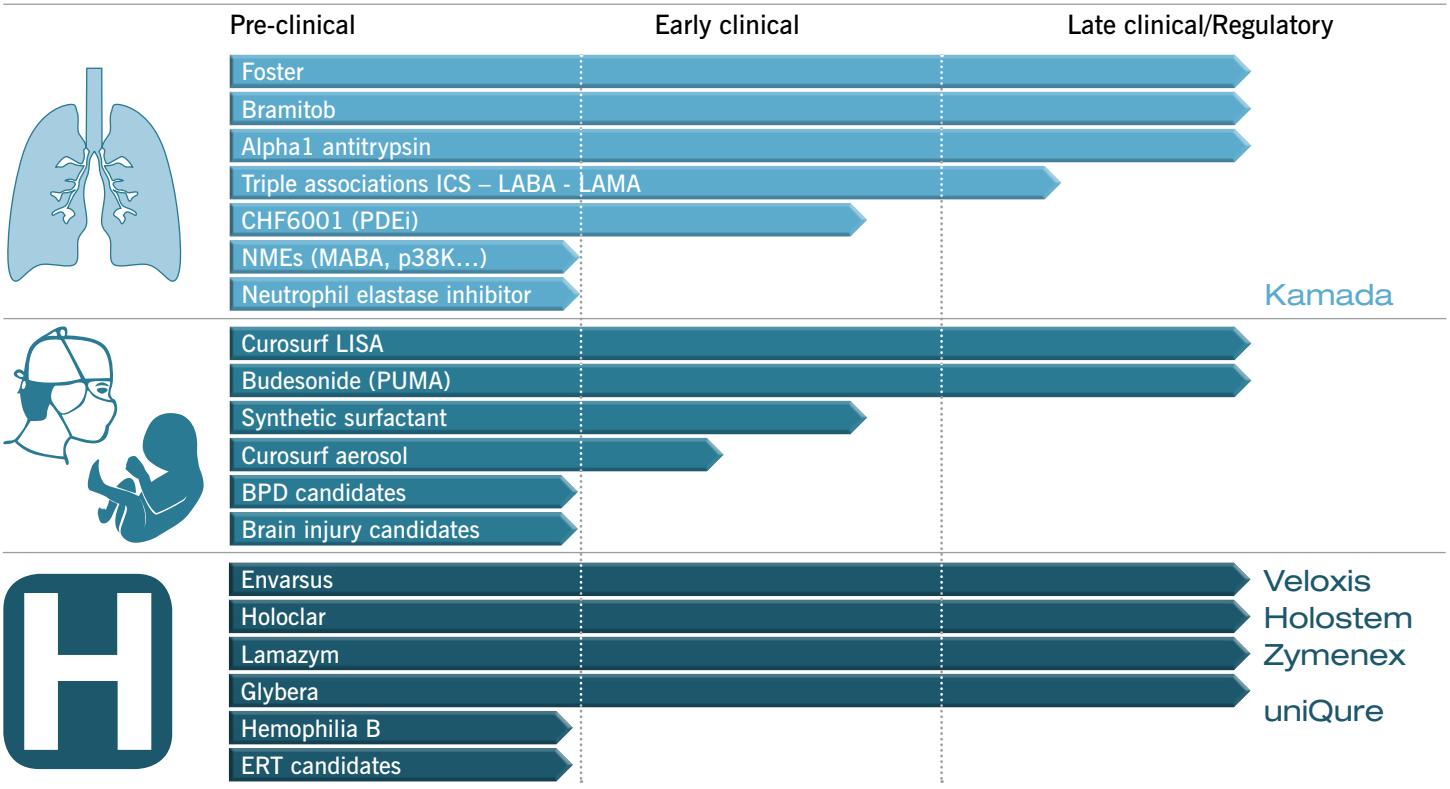
## Continued and significant commitment to R&D

Chiesi continues to be highly committed both to innovative research programs and to fully integrated product development and subsequent marketing approvals of cost-effective therapeutics. In 2013, approximately 13.6% of the Group revenues were invested in R&D representing a total spend of €168 million. Moreover, 70% of Chiesi group revenues were from products generated by and delivered from the internal R&D pipeline.

## An expanding and balanced pipeline, with focus

The number of research programs increased last year with a strong focus in the three key areas: respiratory, neonatology and special care.
At the end of the year there was a total of 26 projects in the pipeline: five discovery programs, nine projects in early development, nine projects in pivotal trials or in the regulatory submission phase and for three projects post-approval R&D commitments were being delivered. This expansion and balance has also been applied to different therapeutic approaches, with the pipeline now including proprietary reformulation of off-patent molecules, novel small molecular entities, peptides, proteins,

## Pipeline overview



gene therapy and cell-based active principles. The plan currently being executed is to expand the number of pipeline projects and to continue the significant investment ensuring productivity targets are achieved.

## Respiratory: continued progress in a critical area for the Company

Foster is a key revenue driver for the future of the Company, but it also remains a very significant element of R&D activity as we roll out a powerful life cycle management program of new dose strengths, dosage forms and clinical indications. 2013 saw four critical Foster milestones successfully achieved:

1. the approval of the marketing authorization application of the currently-approved pressurized metered dose inhaler (pMDI) for the new indication of maintenance and reliever therapy (the so called MART approach),
2. the submission of the marketing authorization application for the new indication of chronic obstructive pulmonary disease (COPD),
3. the approval of Chiesi's new dry powder inhaler (DPI) called NEXThaler for the asthma indication in a further wave of key markets across Europe.
4. In terms of geographical expansion, the roll out of Foster continued with submission of marketing authorization applications in new countries and the very important achievement of approval of the asthma indication in China.

Very positive progress was made with both the pMDI and DPI inhalers delivering a high steroid dose to treat more severe asthma. This included positive regulatory agency interactions, which will facilitate the planned marketing authorization submissions in 2014. This will effectively expand further the Foster product portfolio.

- There is a substantial commitment to a very attractive therapeutic opportunity with our Triple program. Our product candidate which comprises, in a single inhaler, a steroid (beclomethasone) and two different bronchodila-

tors (formoterol and glycopyrrolate) is currently first in class in the industry. We are fully committed to the initiation of a European Medicine Agency-approved phase 3 program.

- The exciting pipeline of proprietary new molecular entities also progressed during the year. These programs include novel anti-inflammatory and novel bronchodilator molecules, and also innovative "double" active molecules comprising two halves to two different pharmacological targets.

## Special care: building on the legacy and commercial value of Curosurf and Bramitob

- Through the clinical success of Curosurf in treating neonatal respiratory distress syndrome, Chiesi has established an impressive platform in neonatology. In this area of high unmet medical need R&D programs include novel and less-invasive methods for the targeted delivery of Curosurf to the lung of the infant. Further progress was achieved for the proprietary synthetic surfactant which is undergoing clinical trials with emerging data supporting the safety, efficacy and clinical utility of this potential new addition to surfactant replacement therapy options.
- As we expand pipeline behind these ground-breaking respiratory-focused products, new programs have been progressed and been added for candidates for the treatment of other neonatal conditions. For example, there are currently no effective approved pharmacological therapeutics for neonatal brain injury: a relatively common condition associated with significant morbidity and mortality of the new born. The program of novel caspase inhibitors has progressed while a program for the development of melatonin was initiated.
- In 2013 the FDA registration of tobramycin inhalation solution sterile, indicated for the treatment of chronic pulmonary infec¬tions caused by Pseudomonas aeruginosa in patients with cystic fibrosis and already marketed in many countries, was successfully completed. This has allowed the launch in the U.S. by Cornerstone Therapeutics under the trade name Bethkis.

## Rare diseases: a transformational year through partnerships and acquisition

- The acquisition of Zymenex, the Scandinavian-based biotechnology company represented a bold step to expand Chiesi R&D with the inclusion of new biologics capability in-house. The leading asset in the Zymenex pipe-

line is an advanced phase 3 enzyme replacement therapy for a rare lysosomal storage disorder: alpha-mannosidosis.

- Two important marketing authorisation applications were filed with European Regulatory Agencies during the year. Holoclar is a groundbreaking tissue-regeneration advanced therapeutic medicinal product which has been developed in partnership with the Holostem company for the treatment of severe injury to the cornea. We also successfully filed the marketing authorization application for Envarsus in partnership with Veloxis. It comprises a once-daily formulation of the immunosuppressant tacrolimus for prophylaxis of solid organ transplant rejection.
- The partnership with Kamada for inhaled alpha 1 antitrypsin also reached a key milestone. The pivotal phase 3 study was completed, which will support the marketing authorization application for this novel delivery format for enzyme replacement therapy in this rare respiratory indication.
- Gene therapy represents another breakthrough approach in therapeutics, and through the partnership with uniQure, Chiesi has now taken an important position in this field. Regultatory approval for Glybera in Europe was secured and we are now successfully engaged in the codevelopment of a targeted gene therapy for haemophilia B, which is soon to enter clinical trials.

## A skilled and dedicated R&D workforce

Our Research & Development team certainly represents a fundamental asset for the business. It comprises integrated functional areas focused on pipeline projects including discovery and pre-clinical research, chemistry manufacturing and controls, drug delivery technologies, clinical development, regulatory affairs, pharmacoviligance, intellectual property, quality assurance, project management and leadership, and R&D portfolio management. Moreover, R&D functions also support already commercialized products through pharmacovigilance and regulatory activities. Headquartered in the purpose-built and fully-integrated new R&D centre in Parma, the team also has important activities in Paris, Chippenham (UK), Rockville (US) and now in Lidingo (Sweden) and Hillerod (Denmark): the latter two sites comprising the new colleagues from Zymenex. The goals of this experienced, cross-functional team are highly-focused on delivery of the pipeline on a global basis and increased productivity to support the growth goals.

# Business Development & Strategic Alliances

The role of Business Development at Chiesi is to complement the internal R&D activities through the acquisition of new products, technologies and know-how developed outside the company.
Of particular interest are projects and products in both the respiratory field and the neonatology area.
In other therapeutic areas, where the Company has yet to develop specific R&D skills, it is Business Development which researches the acquisition of specific know-how (typically by acquiring companies) and that of new products, in this case restricting itself to those in an advanced phase of clinical development.
This applies to Special Care products, an area whose current share of the turnover the Chiesi Group aims to increase.
As part of this strategy, two important agreements were reached in 2013:

1. Exclusive licensing agreement with uniQure for the commercialisation in Europe, Turkey, the CIS, Russia, Brazil, Mexico and China of Glybera, the first gene therapy approved in the European Union. Glybera, which is expected to go on the market in 2014, is indicated in the treatment of Lipoprotein Lipase Deficiency (LPLD). The partnership with uniQure also includes a co-development and licensing agreement for an innovative gene therapy designed as a potential cure for haemophilia B. By reaching this agreement Chiesi has acquired a significant quota of shares in uniQure, a company which as of January 2014 is listed on the NASDAQ.
2. Acquisition of Zymenex, a company specialising in the development of Enzyme Replacement Therapies (ERT) with research centres both in Hillerod (Denmark) and Lindingo (Sweden). This acquisition will bring the Group new skills in the development of biological products: Lamazym, a recombinant enzyme in clinical development phase 3 indicated for the treatment of patients affected by alpha-mannosidosis, and two further products still in the initial development phase for the treatment of two other rare genetic diseases.

In the same period, the Company also finalised an important research contract with a prestigious English university for the development and testing of innovative formulations of melatonin, a natural hormone which may play a significant role in the neuro-protection of newborns exposed to hypoxic-ischemic stress. This agreement is confirmation of the Group's commitment to areas with a high medical need in the neonatology field.

Again in 2013, following the positive results achieved in a phase 2a trial, Chiesi licensed its own molecule CHF 5074 to CereSpir Inc, a start-up based in New York specialising in Alzheimer's. CereSpir has undertaken to complete clinical development of CHF 5074, aimed at obtaining the indication for the treatment and prevention in the initial phases of the disease.
CHF 5074 is considered the first drug in the class of microglia modulators and has demonstrated that it improves cognitive functions and reduces inflammation of the brain in patients with mild cognitive deterioration. Chiesi will work alongside CereSpir to transfer its knowledge and plan the clinical and regulatory activities.

The Group began the process of acquiring 100% of the shares of Cornerstone, a company listed on the NASDAQ, which Chiesi was the majority shareholder of. The process was brought to a close in February 2014, when the de-listing of Cornerstone began,.

At local level numerous agreements were reached regarding the co-promotion of products in the US, Greece, Poland and Turkey.

# Main products

## Foster

A fixed combination of beclomethasone dipropionate (corticosteroid) and formoterol fumarate (a long-acting β2-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 35 countries worldwide, including Russia and China, and further launches are planned throughout 2014. In 2013, Foster obtained the approval of using the MART (Maintenance And Reliever Therapy) posology. Moreover, Chiesi submitted the dossier in order to get approval for the treatment of COPD (Chronic Obstructive Pulmonary Disease).

### Foster NEXThaler

In 2013, in Germany, The Netherlands, Spain, and Italy, the new extrafine powder formulation was launched.

Thanks to the innovative device, NEXThaler, it is positioned as the most suitable to satisfy the need of the patient suffering from persistent asthma. In fact, thanks to the extrafine formulation, the triple full-dose feedback system that guarantees the delivery of the full therapeutic dose and the ease of use, Foster NEXThaler is considered a significant step forward in the treatment of respiratory diseases. In 2014, Foster NEXThaler will be launched in many other Countries, starting from Austria and Belgium.

## Curosurf

An animal-derived surfactant for endotracheal administration indicated in the prevention and treatment of neonatal respiratory distress syndrome in premature infants. This disease is amongst the most common causes of neonatal death and is the result of lung immaturity in preterm newborns.

Its active ingredient is a natural surfactant mainly composed of polar lipids and proteins. Since its introduction in 1992, Curosurf has been used to treat approximately 2 million and 500 thousands newborns. It is the world's leading surfactant, with a 73% market share, and is available in over 80 countries worldwide.

## Atimos

This is a formoterol fumarate 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 β2-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. The licensing of Modulite technology to Novartis confirms its efficacy.

## Bramitob/Bethkis

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. Bramitob 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 has been launched in November 2013 with the brand name Bethkis.

## Brexin

Piroxicam β-cyclodextrin (PBC) is a successful example of the clinical application of "guest-host" technology, which has been awarded the Nobel prize.
The guest is a starch derivative known as β-cyclodextrin, which solubilises the piroxicam host, a non-steroidal anti-inflammatory drug, thereby improving its pharmacological properties.
Piroxicam β-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 sold today in Europe, South America, Asia and Africa

## Clenil

Clenil (beclomethasone dipropionate) is one of Chiesi's historical products and 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 and unit-dose vial for nebulisation).
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 recorded consistent growth.

## Clipper

An oral corticosteroid indicated for the treatment of mild to moderate ulcerative colitis in its active phase.
The drug is available in prolonged-release gastro-resistant beclomethasone dipropionate 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

The value of Glybera (alipogene tiparvovec) is that it treats the underlying cause of LipoProtein Lipase Deficiency (LPLD) rather than symptomatic control.
Patients see a reduction in acute pancreatitis (-60%), relief from strongly debilitating symptoms (pain) and sustained efficacy results.
For prescribers Glybera is the only therapeutic option for LPLD as well as being the first gene-therapy.
For the healthcare system the efficacy of Glybera impacts positively on healthcare budgets (reducing hospitalization, and ICU admission.)

## Iperten/Vivace

This last generation dihydropyridine calcium antagonist (manidipine) 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 (Iperten); Brazil (Manivasc); Greece and Germany (Manyper); Spain (Artedil). Vivace, fixed combination of manidipine and delapril, an ACE-inhibitor, fully developed by Chiesi, is indicated for the treatment of the hypertensive patients not adequately controlled on 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 Italy, Spain and Greece and with the brand-name Hipertil in Brazil.

## Peyona

Peyona (caffeine citrate) is an orphan drug for hospital use only, registered in Europe through a centralised procedure and indicated for the treatment of primary apnoea of premature newborns.
This pathology is characterised by the incomplete development of the brain centres which control respiration.
Apnoea of prematurity is the manifestation of respiratory pauses, which reflect the immaturity of the breathing control systems. Caffeine stimulates the centres that control the central nervous system and has been shown to increase survival rate without neurological deficit, reducing respiratory support and the incidence of bronchopulmonary dysplasia.
The drug is marketed in Austria, Germany, the Czech Republic, Spain, Greece, Holland, Slovakia, the UK, Mexico, Poland, Hungary, Slovenia and Italy. Moreover, during 2013, the product was also launched in Belgium, Columbia, Croatia, Lithuania and China.

# Late stage projects

## Holoclar

A treatment for patients with Moderate-Severe Limbal Stem Cell Deficiency, due to ocular burns. The value of Holocar is that it has the potential to restore sight in this patient group.

## Lamazym

The first enzyme replacement treatment for Alpha-mannosidosis, it replaces the missing enzyme which is the underlying cause of the disease.

# Industrial Operations

The production employs 650 people and takes place at three sites: the Parma production facilities (Italy), with 469 employees, who are split between the San Leonardo and via Palermo plants; the Blois-La Chaussée Saint Victor plant (France), which employs 67 people; the Santana de Parnaìba plant (Brazil), which has 114 employees.

## Parma

The Group's most important production plant is also an international supply centre and exports to over 60 countries. The San Leonardo plant operates under the ISO 9001:2008 Quality Management System Certification and has passed many inspections carried out by the regulatory authorities of a number of countries, including the US Food and Drug Administration, the Canadian Therapeutic Products Program, the Chinese CFDA, Russian GMP & Quality Management Inspectorate, the Brazilian Health Agency A.N.V.I.S.A. and the Agenzia Italiana del Farmaco.
A Health and Work Safety Management System complying with British Standard OHSAS 18001:2007 and an Environment Management system in accordance with ISO 14001:2004 have also been implemented and certified.
The proper application of international Good Manufacturing Practice standards, achieved using avant-garde technologies, represents the best way to guarantee worker safety and respect for the environment.
Annual production in Parma is over 52 million sales units.
The San Leonardo production facilities prepare solid form drugs: tablets and pow-

ders for DPIs (Dry Powder Inhalers); solutions and suspensions either for pressurised MDIs (Metered Dose Inhalers) with eco-friendly propellants (HFA) or sterile unit-dose vials (UDV) with Blow-Fill-Seal technology (BFS) for use with a nebuliser.
Current 3-shift production capacity for sterile UDV nebulisation vials stands at 210 million units (vials) per annum. MDI double shift production capacity is in excess of 25 million canisters, with further successfully trialed potential capacity using a third shift. The via Palermo production facilities prepare vials of sterile suspension for endotracheal administration (Curosurf) and liquid form pharmaceuticals such as drops, syrups and nasal sprays. The 2006 expansions made in the Curosurf sterile suspension production department, which have been approved by European health authorities and the US FDA, along with those made at the plant supplying the active ingredient, have increased capacity to over 530,000 units. Due to growing sales of the product, plans have already been approved and begun for further significant expansion in new production departments, both for the active ingredient and the drug. In addition, an automatic filling and assembly line for a new Dry Powder Inhaler (Nexthaler) is also ready and has already produced several hundred thousand units, which also includes the packaging line with a capacity of 4 million sales units, is operational.
Production and support processes (Cleaning in Place, Sterilising in Place) are managed and monitored by approved IT systems. In order to further increase the level of automation, Manufacturing Execution System (MES) type IT architecture has been put in place. The IT dispensing system has been linked to this, whereas the electronic batch record, already operative in the sterile UDV and pMDI departments, is now being extended to the other departments.
The Engineering department in Parma has made a fundamental contribution to the creation of the new Research Centre and its approval from the various authorities concerned and is now engaged in the requalification of the via Palermo Site, in the construction of Curosurf new departments for the active principle in Modena and for the Drug Product in Parma, and supporting the French Plant in Blois in the construction of the new Dry Powder Inhaler (Nexthaler) Department.

## Blois

Production at the Blois facilities stands at over 7 million sales units, which are mainly destined for the other affiliates in the Group. The French production labs specialise in capsule and tablet blister packaging and also in the final assembly and production steps for MDIs, which can then be deposited in the ample refrigerated storage facilities at the plant.
The analytical transfer activities have been completed to authorise the Blois plant to check and release batches.
The plant is also equipped for direct distribution to the client for both the French and export markets.

Lastly, a new department is being created under completion for the production, packaging, checking and storage of the new Nexthaler Powder Inhaler to assist the existing one in Parma.

## Santana de Parnaìba

These facilities produce over 11 million sales units. The production lines prepare solid pharmaceutical forms (tablets), liquids, solutions and pressurised suspensions for inhalation (MDI) formulated for use with eco-friendly HFA propellant.
Aside from the local market, these products are destined for those of the Group's other affiliates, including Italy and the UK, as a result of AIFA approval (Italian Agency for Pharmaceuticals) following regular inspections on site, and for export to licensees and distributors

## Technological Support and Corporate Industrial Governance

The Corporate Manufacturing Technology, Corporate Engineering, Corporate Quality Operations, Corporate Logistics and Corporate HSE departments are able to support:

- Research and Development in scaling up developed products;
- production transfer between facilities inside or outside the Group;
- partners, when they produce directly using technologies patented by the Company.

In addition, they are able to support:

- the due diligence activities for Business Development;
- the technological lifecycle management of existing products.

The Corporate Production function ensures that *Lean* techniques are made widely available throughout the Group's facilities to guarantee maximum productivity.
Lastly, Corporate Industrial Management Control oversees the Group's budget, product-costing and Industrial Reporting processes and also supports the economic assessment of the other corporate functions' activities, as well as managing production outsourcing.

# 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, we have 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 its 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, guarantees the distribution of the drug throughout the entire bronchial tree, thus ensuring uniform treatment of inflammation and bronchoconstriction 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 mainly consists 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, which can be potentially life threatening. The commitment in this area is considered strategic for the Group's future and potentially of great social impact. Aside from its longstanding commitment to the treatment of respiratory distress syndrome (RDS), a field in which the surfactant Curosurf has become the international gold standard, the company now also commer-cialises Peyona for the treatment of apnoea of prematurity and is looking into other neonatal diseases, including bronchopulmonary dysplasia. It wants to offer the medical and scientific com-munities new therapeutic options for the treatment of serious genetic diseases such as cystic fibrosis. There have been two steps in this direction: the first was the launch of Bramitob and the acquisition of Hyaneb for the treatment of cystic fibrosis patients, and the second was to set up a joint initiative with physicians and associations to improve the management of patients affected by this disease.
It should also be remembered the European expected approval of Envarsus, indicated for suppression of the immune response to prevent the rejection of transplanted solid organs.

## Rare Diseases

Patients with rare diseases typically face a number of issues including, a lack of access to correct diagnosis, information, scientific knowledge with poor social consequences (stigmatization) and appropriate quality health care. Chiesi is currently involved in three main areas: LipoProtein Lipase Deficiency (LPLD), an extremely rare disease with 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 and Alpha-mannosidosis chronic, ultra-rare, genetic disease characterized by progressive worsening of manifestations and mental and growth retardation. The current Chiesi Rare Disease franchise has three key products in the portfolio: Glybera, Holoclar and Lamazym.

# Global Marketing

## Sponsorship

The Chiesi Group supports many scientific activities and actively participates in some of the most important medical-scientific congresses in its therapeutic areas of interest.

| RESPIRATORY | |
|---|---|
| **European Respiratory Society (ERS)** | The ERS is the leading professional organisation in its field in Europe. Its scope covers both basic science and clinical medicine. Chiesi is one of the major sponsors of the ERS congress, a meeting hosting over 22,000 physicians interested in the respiratory field. |
| **American Thoracic Society (ATS)** | The ATS mission is to improve health worldwide by advancing research, clinical care and public health in respiratory disease, critical illness and sleep disorders. Chiesi is a sponsor of the ATS congress. |

| CYSTIC FIBROSIS | |
|---|---|
| **European Cystic Fibrosis Society (ECFS)** | The ECFS provides an international forum on all aspects of cystic fibrosis and fosters the best possible care for people with cystic fibrosis. |
| **Cystic Fibrosis European Masterclass (CFEM)** | The aim of this Masterclass is to provide clinicians and researchers with state of the art updates on developments in our understanding of cystic fibrosis and how to deliver the best care possible. Chiesi is the only Pharmaceutical Company supporting this highly scientific event. |

| RESPIRATORY DISTRESS SYNDROME | |
|---|---|
| **Curosurf Family Meeting** | 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 attend only by invitation. The first edition of the Curosurf Family meeting was held in 1986; over the years, it has become a worldwide reference point for research into the surfactant field. |
| **European Society for Paediatric Research Congress** | This is the most important European paediatric meeting with a focus on neonatology. The sponsorship agreement includes, alongside the ordinary congress activities, the Robertson Award for Neonatal Lung Research and the Neonatal Lung Symposium, both sponsored by an unrestricted educational grant. |
| **European Society of Neonatologist Courses** | Chiesi is the only sponsor of a two-day post-graduate course prior to the ESPR Congress, an interactive course with top level researchers, creating a partnership with the new generations of specialists. |

# Donorship

## Respiratory Distress Syndrome

The Curosurf Team continue also in the 2013 to support two projects in Cambodia and Burma:

| | |
|---|---|
| **Cambodia Innocent Prisoners, - *"The knot" a No Profit international association*** | The objective of the project is to assist pregnant women in prison and children who are living in prisons with their parents because they have no better alternative. |
| **BURMA: The Health Paediatric Centre - *"A Helping Hand For Children" an Italian No Profit association*.** | The aim of the project is to provide free health care to the children of Mobye Parish community, in Myanmar (Burma), an area without hospitals reachable by foot. |

## High level donorship

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

| | |
|---|---|
| **Global INitiative for Asthma (GINA)** | The Global INitiative for Asthma (GINA) works with health care 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 health care professionals and public health officials to raise awareness and to improve the prevention and treatment of Chronic Obstructive Pulmonary Disease (COPD). |

## Patient Organisations

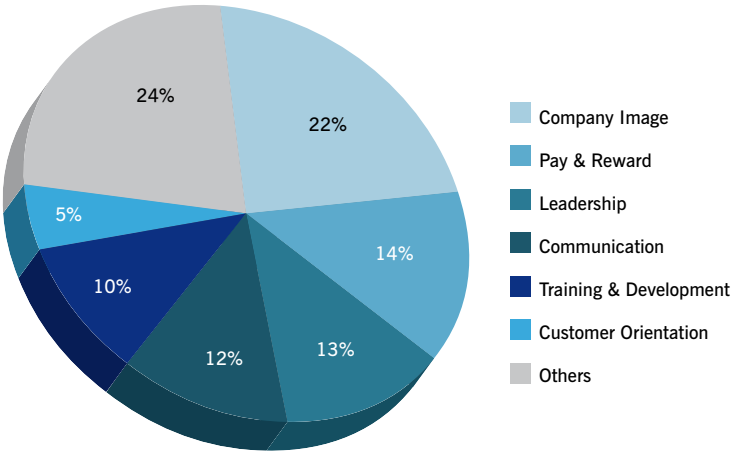
Chiesi Group supports the following international organizations:

| **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 formed by European patient associations would be a more effective way of meeting the needs and safeguarding the rights of patients and their carers. |

# Human Resources

The evolution of the internal survey "Chiesi Voices" has continued to characterize the activities of Human Resources for the entire 2013. Based on the suggestions collected through the survey, in-depth meetings were initiated in all subsidiaries of the Group, which was attended by cross-functional teams made up on a voluntary basis and with the coordination of HR departments. The discussions started up during these meetings led to enact more than 280 improvement actions focusing on the most diverse company reputation, leadership, customer focus, people management, communication, training, remuneration policies just to name a few. At the end of 2013 107 actions had already been completed, demonstrating the vitality with which the cross-functional teams set improvement programs. The success of the program is also attested by the fact that many of the follow-up meetings will be repeated to verify the birth of new needs and implement new programs for improvement.

## Distribution by topic of internal improvement actions promoted as a follow up of the internal survey "Chiesi Voices"




The process of regionalization, started in 2012 and which led to the establishment of three macro-regions (Southern Europe, Northern Europe, countries outside Europe), is helping to establish a positive closeness between subsidiaries and headquarters functions and to meet the diverse needs of markets. The Region Emerging Countries carried out a survey involving, in addition to the general manager of all the non-European countries, their management of the Sales & Marketing, Finance and Human Resources departments. The initiative, which aims to assess the functioning of the regional model and optimize processes, is expected in 2014 for the North Europe Region. During the same period the Region South Europe will involve all its committees in a Team buiding program for addressing the issues of Leadership and Decision Making in a context of uncertainty.

The augmented proximity between the various Group entities has allowed us to create even more favorable conditions for international mobility. The definition of the policy that governs international assigments has helped to clarify in a consistent manner and the way of implementation of expatriation, both the management of expatriates. At the same time the launch of the new governing international job posting allows people working for the Company to apply to open positions in all branches, thus having the opportunity to follow their own desires and career aspirations. The international assigments activated in the last 18 months were 21, in addition to 42 internal job posting: experiences abroad are now a reality in

full growth within the Group. Similarly, the skills required by disciplines such as enzyme replacement therapy, gene therapy and regenerative medicine within the Group are bringing new researchers, experts in drug registration and marketing procedures that enrich the organization of cutting edge, specialist know-how.

The participation in Top Employer led Chiesi Farmaceutici Italy, subsidiaries in France, Spain, Germany, the UK and, for the first time, Poland to obtain this important recognition, confirmed by the prestigious title of Top Employer Europe.

Chiesi Academy confirms initiative fully viable. The third edition of the Chiesi Corporate Master, in collaboration with SDA Bocconi, was initiated by introducing a particularly relevant innovation in terms of internationalization: non-European colleagues appear for the first time among the 33 participants, from Brazil, China, Pakistan, and Turkey. The enduring success of the CCM is the most explicit confirmation of its educational value.

Similarly, the *Development for Executives and Leaders project* (DEAL), a Chiesi Academy initiative aimed at managers who occupy top positions, came in 2014 to its second edition. The hallmark of DEAL project is the strong international profile, both in terms of participants (also in this case, participation is extended to colleagues from locations outside of Europe), and of faculty and teaching sites.

Both courses are focused on general management skills, with particular attention to the pharmaceutical world. Numerous lessons are taught by exponents of the corporate top management.

# Information & Communication Technology

## The evolution of the Information System Governance model

Evolution on an international scale and a push for the development and commercialisation of global products have represented a constant focus for the Group in the last few years. This has created the increasingly pressing need for an integration programme between the Corporate ICT function and the corresponding functions of the affiliates, in order to be able to provide homogenous and consistent solutions for the needs of the main business processes.The governance model for the information systems is therefore being redefined to make it uniformly standardised for the whole Group. Its main objectives include:

- strengthening the business partnership
- focussing on ICT processes (needs managing, project, implementation and functioning of systems)
- developing the ability to put innovative solutions into practice.

## SAPiens project

After more than a year since its launch in Italy, the SAP system now forms part of the daily activities of the whole organisation. In 2013 the system underwent a stabilisation process, which enabled all of its users to gain a better understanding of its functions. In addition, the system was gradually completed by means of evolving maintenance activities. At the beginning of 2014, the SAPiens project received the SAP Quality Award (Gold Winner), which was assigned by SAP Italy; this achievement means that the project will take part in the related competition for the Europe and Asia Region.
The roll-out phase is currently underway, which will involve the implementation of SAP in the Group's affiliates. The process of introducing the system in France and the UK, which began in 2013, will be completed by the end of this year.

## Nomos Project

The architecture of new technological infrastructures represents a fundamental element within the new governance model. The Nomos project, which concerns the whole Group, aims to define the common standards and guidelines for all the components of this infrastructure. The ICT functions of the affiliates will be pivotal for its success.
Over the course of 2014, the project, set up at the end of 2013, will define the criteria for the selection, introduction and management of the main technological components, such as the network infrastructure, security parameters and storage systems.

# Biotechnology: a paradigm for the development of innovative therapies

Alessandro Sidoli

President of
Assobiotec-Federchimica

Just over than thirty years ago the first biotechnological drug, human recombinant insulin produced using genetically modified bacteria, was introduced to the market. Since then, almost 200 innovative biological, or biotechnological, drugs have been made available to the physicians, and more than 325 million patients have benefitted from the remarkable contribution of biotechnologies not only to the therapy, but also to the diagnosis and prevention of a number of extremely relevant diseases, both from a clinical and epidemiological point of view. Indeed, more than 40% of the drugs currently under development are biotechnological compounds: monoclonal antibodies, recombinant proteins, DNA or RNA products, cell or gene therapies, regenerative medicine products. A broad range of molecules and therapies for the treatment of oncological, genetic, inflammatory, autoimmune or metabolic diseases and – last but not least – of several neurological and degenerative disorders which are becoming more and more critical, particularly in western countries, due to increased life expectancy of the population.

As the result of a revolutionary research paradigm, that allows translating the in depth insight of the genetic and molecular mechanisms into therapeutic innovation, biological drugs enable us to take a radically new approach to tackling the treatment of a number of unmet medical needs and many Rare Diseases. The core of this revolution, leading to new models of personalised medicine, or rather new therapeutic approaches specifically tailored to the characteristics of the individual patient, is to be found in the radically new prospects associated to the definition of the DNA structure, that pivotal discovery made by Watson and Crick, whose sixtieth anniversary was celebrated throughout all Europe in the course of the 2013 European Biotech Week.

The sequencing of the human genome, the understanding of the genetic and molecular bases of often seemingly different diseases, and the countless tools provided by biotechnologies allow the biopharmaceutical industry to develop innovative therapeutic approaches, selectively aimed at specific pharmacological targets, as well as to anticipate their effects on a particular patient population and to optimize the entire pathway of cure.

In fact, the innovation drive of biotechnologies has been also exploited in diagnostics, leading to the development of new detective, quantitative and predictive methods, that by accurately and promptly identifying the causes of disease, allow both the correlation between diagnosis and therapeutic schemes specifically customized on patient's characteristics, and the steady monitoring of therapy in terms of effectiveness. This specifically

applies to the so-called *omics* technologies, which have made a decisive contribution to the identification of *biomarkers* that can be used to establish a patient population eligible for a specific treatment, or to forecast the adverse effects on another, or like litmus paper for therapy monitoring.

Recently introduced in the EMA guidelines as genetic reference endpoints in the initial development phases of a new drug, *biomarkers* also make it possible to set up these same clinical development programmes in a more targeted and rational way, thus optimising time and expenditure. This introduces another fundamental consideration about the contribution of biotechnologies to ensuring better allocation of the invested resources, with regards not only to improving the quality of treatments and the efficiency of the healthcare and welfare systems, but also the productivity of the R&D processes themselves.

**Indeed, constantly increasing investments, extended timeframes needed for the development of a new drug and the high business risk profile inherent in such activity, combined with its reduced profitability, urges the pharmaceutical industry to optimise the entire R&D process, which requires increasingly higher and more complex levels of expertise and specialisation.**

Thus, innovation goes beyond companies' boundaries and spreads through a collaborative network, based on a model of *open innovation* which brings different realities (academia, industry, charities, etc.) to share their respective skills and know-how in an effective and synergistic way.

It is precisely in this context that biotech firms have been the key players in another genuine revolution. In fact, nowadays, in almost 80% of cases innovation originates outside *big pharma's* research laboratories, through the acquisition of ideas, technologies and projects which stem from specialised public or private research centres, or smaller yet highly dedicated firms, such as biotech companies. This is now a consolidated approach by which, freed from the limits of a development model exclusively based on resorting to internal skills and resources, drug companies can feed their own product pipelines and cope with the drop in research productivity.

Actually, the continuing increase in R&D investments by *big pharma* (+10% per year) does not correspond to a similar growth in the number of new molecules coming onto the market. Analysing data concerning the number of new molecular entities and biologicals approved each year by the US FDA from 1996 to 2013, this figure has dropped from 59 to 27, despite the fact that since 2011 the number of approvals has on average begun to grow once again[1]. Nonetheless, it is interesting to note that more than a third of the drugs approved in the last decade are biological ones[2]. Furthermore, most of the molecules coming onto the market today are for the treatment of *unmet medical needs*, and many of them have been assigned *orphan drug* status, and the same number of

personalised medicine products is by now significant[3].

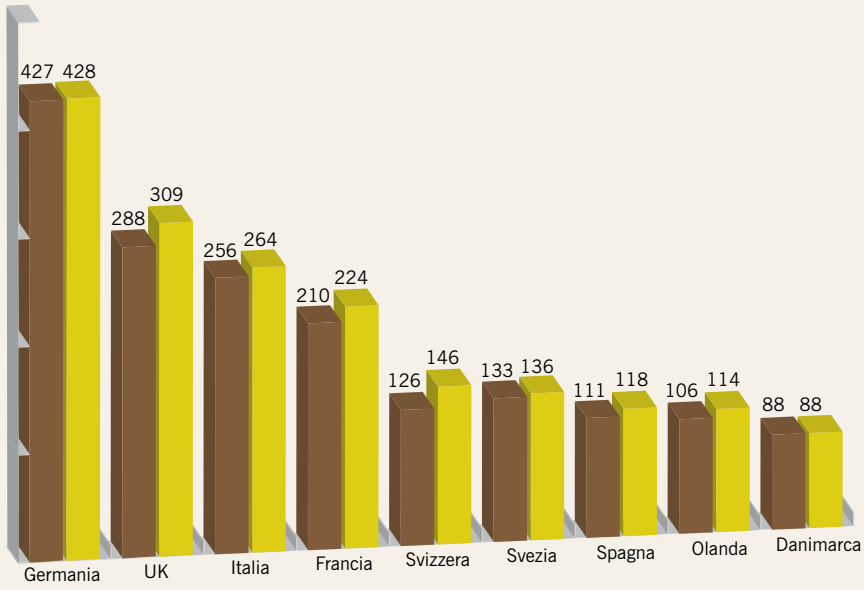
In Italy, too, biotechnological research is associated with an extremely competitive industry. In spite of the difficult economic international situation and the many weaknesses of our industrial system, particularly in respect of access to adequate R&D financing, Italian biotech firms are demonstrating a surprising ability to grow and optimise investment in terms of value creation. Their strength without doubt lies in the extraordinary potential of biotechnologies, as well as the quality of our scientists, whose levels of productivity and merit are unanimously recognised, as is the determination and long-sighted vision of our entrepreneurs and managers.

Data from the 2014 Italian Biotechnology Report, edited by Ernst&Young and Assobiotec, confirm once again our Country's position is in third place in Europe for the number of dedicated or *pure* biotech firms (Figure 1).

Equally as important is the fact that the levels of scientific excellence achieved by Italian biotech companies are further confirmed in a number of cutting-edge areas of pharmacological research, such as Advanced Therapies and Rare Diseases. It is in precisely in these areas that not only does the competitiveness of our biotech companies fully emerge but also the complementary role they have alongside pharmaceutical companies: another key aspect which highlights the potential of the entire system of Italian industrial research in the field of biopharmaceuticals.

Those such as the Chiesi Group represent a true point of reference in this sense, both for the important results achieved by the company on a global scale in terms of presence and turnover, and for its significant and constant commitment to R&D, with a percentage investment of its turnover which puts it in first place among Italian pharma companies, and twelfth among those in Europe. This dynamism is further proven by the farsighted policy for strategic alliances, licensing agreements and acquisitions in the field of regenerative medicine and gene therapy, transplant rejection which will provide the Group with key opportunities in the most advanced areas of medicine in the future.

**Figura 1.**
**Number of pure biotech firms in the main European countries**




(Source: Ernst & Young)

Note

1 Nature Reviews Drug Discovery, Volume 13, February 2014

2 PhRMA, Medicines in Development – Biologics, 2013 Report

3 Ernst&Young, Beyond borders, Biotechnology Industry Report 2013

# Regenerative medicine comes of age

Gilberto Corbellini

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Sapienza University of Rome

"Regenerative medicine", as it is known, deals with two issues. In the past three decades progress has been made both with basic biological knowledge and technologies to understand and intervene in molecular and cellular mechanisms controlling the functions of tissues and organs. These developments have made it possible to come up with strategies to treat degenerative processes or lesions causing structural and functional damages, which it was not possible to treat with synthetic chemical components alone. By exploiting the fact that a number of tissues constantly renew themselves throughout the course of life, regenerative medicine aims to design cellular, tissue or gene therapies to restore either completely or partially the proper functioning of organs compromised as a result of genetic anomalies and/or traumas and degenerative processes of various types.

The regenerative medicine approaches also provide unusually timely answers to a new kind of health issues, dictated by an emerging and challenging epidemiological picture. The successes achieved by diagnostic, therapeutic and preventive/rehabilitative medicine have extended our life expectancy and increased the prevalence of degenerative and/or rare diseases. Even developing countries have begun to record a rise in chronic degenerative diseases, and in particular in diabetes, cancer and neurological disorders; diseases which in the industrialised world tend to arise more frequently after the age of sixty-five/seventy. The phenomenon of population ageing inevitably goes hand in hand with an increase in healthcare expenditure, where neurodegenerative and oncological diseases have begun to represent the areas with the highest economic and social cost.

Despite the general excitement surrounding the stem cell question, which unfortunately results in the publicising and promotion of pseudo-therapies to the detriment of deceived patients, along with hundreds of thousands of clinical studies, the only regenerative therapies to date that work are those using blood cells (bone marrow transplant) and epithelial cells (skin and cornea).

All the available scientific, epidemiological-healthcare and economic analyses nonetheless point to a successful future for regenerative medicine. However, a report on regenerative medicine published last July by the British House of Lords Science and Technology Committee7 underlines that the term characterising the extensive investigation carried out into the development prospects for this sector is "uncertainty", in particular regarding the economic return that can be expected in light of the investments needed to develop regenerative therapies of clinical interest. Yet the report does not provide clear answers, aside from its proposal to organise the activities already underway

Note

1 http://www.publications.parliament.uk/pa/ld201314/ldselect/ldsctech/23/23.pdf

in a more efficient way, and a call for political commitment to eliminate several obstacles and smooth the route "from bench to bedside". Little attention is paid to the lack of basic knowledge, i.e. that which provides the conditions necessary to reduce uncertainty.

It is unlikely in the short term that the field of regenerative medicine will bring about the same successes achieved in the development and use of drugs deriving from the traditional model of evidence-based medicine, which develops and provides for treatments to be approved by testing them empirically against a placebo and/or an active comparator. Furthermore, reducing the spatial-temporal distance between the laboratory and the patient's bedside, as translational medicine does, only provide a partial solution. The biopathological processes in which regenerative therapies intervene are more complex and variable compared to those that may be targeted by traditional drugs. It follows that knowledge available from previous experimental investigations, or in any case the biological rationale of an intervention aimed at restoring a physiological function as a whole by administering medically-manipulated biological preparations, should carry as much weight as the preliminary empirical evidence obtained in the lab on animals models or in vitro. Namely that the 'clinical trials' carried out on mice or cells can only be taken seriously if they generate biologically plausible hypotheses, which can be tested, and if need be falsified through clinical experimentation. The current approach which says "as we have some stem cells either made or deriving from somewhere, let's try to administer them to a patient and see what happens", merely risks of creating hype and irrational expectations, which then feed stem cell sensationalism and tourism; that is to say it increases the risk of a contagious epidemic of the

Italian Stamina-like cases. We should also remind ourselves that it is a rather counter-educational method of ensuring that medicine continues to have a sound epistemological basis.

It is easy to understand that investments made in basic bio(techno)logical research are riskier than those made in drug chemistry, and economic incentives are therefore needed to attract private businesses as well. Risk capitals, as economic analyses of the investments made in this sector show, risk little or are prudent for the moment. In truth because they see no rationally designed development strategies. If we want businesses to contribute investment to these therapeutic methods, which is the required and appropriate condition because it is through regulated competition that a rapid technological evolution, a reduction in costs and therefore greater accessibility to regenerative therapies can be achieved, creative solutions must also be conceived at patent level. I know this is heresy, but I believe that we should begin to consider the possibility of providing some form of economic compensation for basic findings discovered in private labs, findings which demonstrably allow significant technological progress in the regenerative medicine field.

Applying biological plausibility at pre-clinical level, in other words by defining the rationale of the operation being proposed, within the scope of the development procedures of a regenerative therapy, the regulatory restrictions could be redesigned, restrictions which in western countries are currently inadequate and disadvantageous in respect of the type of therapy whose safety and efficacy is to be tested. Tis is to say that in the face of pre-clinical evidence which attests to the safety or risks that are acceptable and consciously accepted by the patient and a valid biological rationale falsifiable by clinical experimentation, conditional use of the therapy should be allowed on the basis of criteria nonetheless defined by independent regulatory agencies. The European Medicines Agency (EMA) strategy also seems to be moving in this direction (EMA) if we think of Glybera, the first gene therapy approved in Europe also thanks to the contribution made by the Italian members of the Committee for Medicinal Products for Human Use (CHMP).

To conclude, there are reasonable arguments to believe that the success of regenerative medicine will depend on greater investment to bring more basic science to medicine that is to medical and healthcare culture. This implies defining improved collaborative strategies between public and private investment, and also adapting the rationale behind regulatory procedures to these new conditions.

# CHIESI WORLDWIDE

SOUTH EUROPE

NORTH & CENTRAL EUROPE

EMERGING COUNTRIES & INTERNATIONAL COMMERCIAL OPERATIONS

OUR OFFICES

## SOUTH EUROPE

# Pharmaceutical Division Italy

The Pharmaceutical Division Italy has performed beyond market levels for the eighth consecutive year, confirming its position as leader in the respiratory sector. Chiesi's rate of growth recorded by IMS stands at +1.7%, in a market up by 0.4% on 2012.

These results were achieved thanks to product quality, the intrinsic value of the brand, the work done by all those in the division.

| Italy | |
|---|---|
| Domestic direct Sales (K€) | 283,556 |
| Variation versus 2012 | 7.7% |
| Human resources | 1,560 |
| Commercial network | 454 |

In 2013 the division was restructured to develop a new relationship with the intermediate channel and chemists. This internal reorganisation also involved creating a new Sales & Distribution Business Unit, joining the two general Master lines of the Primary Care Business Unit, and modifying the structure of Market Access. The Hospital Business structure was created within the Special Care Business Unit to ensure a greater focus on the hospital channel.

Primary Care performed extremely well, achieving a growth rate of 9.2% compared to 2012, in an increasingly difficult scenario not only because of competitors but also pharmaceutical cost containment measures.

The respiratory area represents the driving force in the portfolio: Foster, Clenil A, Fluibron A and Hirobriz have grown faster than the reference markets thereby increasing respective market shares.

In October 2013 Foster Nexthaler device was successfully launched, completing the available formulations for the treatment of asthma sufferers.

In this area, Chiesi has for some time been the leading company in the Italian market in terms of units sold; since the latter half of last year it also has the highest sales figures. These results confirm our supremacy in Italy in the respiratory field.

Results have been less favourable in the cardiovascular area with Provisacor and Delapride, whose respective markets are now dominated by generics.

Special Care ended the year positively with a 2.7% increase on the previous year. Clody maintains its position as injectable bisphosphonate market leader with a growth rate of 5% compared to the previous year.

Positive results were also achieved both in the gastroenterological area, with a performance beyond market levels, and the neurological area with Jumex, which remains a top performer.

In spite of decreasing birth rates and hospital healthcare cost containment, the neonatology area remains a key sector for the Company now and in the future.
In thalassemia, the new formulation of Ferriprox 1000 mg, which was launched in 2012, completes the range of formulations available on the market.
2013 also saw the launch of two supplements, Donegal Plus, which completes the osteoarticular portfolio, and Skatto Q10, an innovative coenzyme Q10 formulation.
The year ended positively for the product range assigned to the new Sales & Distribution Business Unit, which recorded an increase of 2.4% compared to the previous year, thereby validating the organisational decisions taken.
The acquisition of the Novadynamics business branch means that the devices and supplements promoted by this business partner's agents now form part of portfolio.
Furthermore, a new Business Unit has been set up to manage the mature products in the OTC, SOP and device portfolios, in addition to the entire range of Chiesi products in the supply chain: wholesalers, cooperatives and chemists.
Other products performing particularly well were Clenil Compositum, Flomax and the OTC formulation of Fluibron, which has increased both compared to the reference market and in terms of market share.
In the cardiovascular area, characterised by a relevant presence of generics, the branded products Iperten and Triniplas have increased their market share.
The results achieved during the internal audits have certified the commitment of the Chiesi teams, and highlighted as key strengths the commitment of the management, sense of belonging, team spirit and the pro-active approach of the process owners. This achievement confirms both skills relating to products, therapeutic areas and diseases, and the importance attributed to doctors and patients with an ethical approach to the business.

# Chiesi France

Chiesi SA was still impacted by a depressed pharmaceutical market evolution driven by dramatic price cuts and 2012 measures to influence positively generics penetration.
Despite of this context, our respiratory products representing more than 70% of our turn over, have grown by 8% vs last year. At the end of last year, our team has successfully launched the MART indication for Innovair, reinforcing the expected growth for the beginning of this year and preparing NEXThaler launch.
Rinoclenil maintained significant growth levels, gaining more than 5% of the market share in its second year since the launch.
In the Special Care business, Curosurf met its objectives and reached 2% growth.
2013 was an important year for the Blois production

| France | |
|---|---|
| Domestic direct Sales (K€) | 101,106 |
| Variation versus 2012 | -4.6% |
| Human resources | 310 |
| Commercial network | 160 |

plant. All the affiliate's teams have been involved in the recent building project for the extension of the NEXThaler project (€ 11.5 million invested), including those concerned in the Corporate division.
The construction work will be finished by the third quarter of 2014.
Production levels have increased to 7.1 million packages based on bulk coming from the Parma and Sao Paulo plants and our third parties located in several European countries.
From an IT point of view, SAP is now entering into its second phase (training, test and final migration).

# Chiesi Spain

Chiesi Spain's results have been positive both in terms of revenues and EBIT, despite the difficult year for the Spanish pharmaceutical market. Revenues reached € 71.4 million, with an increase of 24.5% and a growth in terms of market share. This increase was obtained thanks the new launches and licenses (Prevencor, Foster Nexthaler, Hyaneb). Some core products have also contributed to significant growth (Flogoprofen and Foster)
The affiliate has maintained its structure with around 230 employees, 180 of whom represent sales force distributed between three business Units: Retail, focussing on general practitioners and specialists; Special Care, focussing on hospitals; and Farma, focussing on Pharmacy sales.
The Special Care Unit focusses its promotion on the hospital market with products like Clipper, Bramitob, Curosurf, Peyona and Hyaneb, launched in May 2013.
In September 2012 the business unit was created in order to promote Chiesi Spain OTC products in a competitive market. During its first year, the business unit successfully achieved its goals, and currently represents 25% of the affiliate's total sales.

| Spain | |
|---|---|
| Domestic direct Sales (K€) | 68,085 |
| Variation versus 2012 | 24.5% |
| Human resources | 231 |
| Commercial network | 182 |

In September 2013 the Spanish affiliate launched Foster Nexthaler. The product was eagerly awaited by the physicians due to the strong acceptance of the powder inhalers in the Spanish Respiratory market. The launch was successful thanks to the commitment of all the employees and to the excellent performance of the Foster team and retail reps.
A far as the employees are concerned, the Company has also continued investing in team development and growth.
The aim for 2014 is to continue strengthening our presence on the market, position the affiliate among the best performers in the respiratory, cardiovascular, neonatology and OTC fields and achieve an excellent performance & results with the new challenges to come.

# Chiesi Greece

Even if 2013 was the 6th year of recession for Greece, Chiesi Hellas once again achieved a record of sales. A turnover up by 30% on the previous year was a truly significant achievement.
The local pharma environment remains unpredictable and continually presents "surprises", mostly in pricing and reimbursement; Chiesi Hellas people capitalised on these changes as a steering wheel for continuous innovation in all their entrepreneurial activities. Joint initiatives and synergies with major local Greek companies combined with the commitment of the
employees to a result-oriented approach, were the main success factors for the affiliate.
At the end of the year, the Company was in 36th position in the IMS ranking, gaining eight positions on the previous year and exceeding by far the target set!
The Foster brand, its main product, is among the top 150 brands in the pharmaceutical market, while mature brands like Manyper and Vivace are leaders in volume growth in their therapeutic classes. Having also gained almost 100% of the neonatal market for Peyona & Curosurf, the affiliate is proud to offer the best solutions in this sensitive therapeutic segment.

| Greece | |
|---|---|
| Domestic direct Sales (K€) | 17,531 |
| Variation versus 2012 | 30.4% |
| Human resources | 61 |
| Commercial network | 40 |

# Chiesi Belgium

In 2013, Chiesi Belgium was able to build further upon the previous year's success. Despite the downward trend in the market and governmental measures such as price reductions, this young affiliate achieved ambitious growth rates. Revenues increased by almost 13% reaching € 15 m.
The progress is mainly driven by the top product Inuvair, which continues to increase market share, (16% in the fixed dose-combo market), and achieving 13% growth rate compared to year. Furthermore, Chiesi Belgium has reinforced its image as an important player in the Belgian respiratory market and is well regarded by practitioners and specialists in particular.
In the neonatological maret, Curosurf further strength-

| Belgium | |
|---|---|
| Domestic direct Sales (K€) | 14,672 |
| Variation versus 2012 | 12.5% |
| Human resources | 37 |
| Commercial network | 37 |

ened its market leader position by growing more than 40%, while Clipper showed substantial progress in terms of market penetration.

2014 will be a milestone for the Belgian affiliate. The launch of Inuvair Nexthaler will make a significant impact on the sales and will contribute to the innovative image of Chiesi as a respiratory partner in a dry powder inhaler-driven country.
The aim of the year – to lay the foundations for a mature growing company – blends with the initiatives of global integration, the development of people and talents aimed at enhancing cross-functional collaboration, efficiency and the achievement of results.

## NORTH & CENTRAL EUROPE

# Chiesi United Kingdom

2013 saw the UK affiliate reach unprecedented results in terms of sales, with annual sales £ 110 million.
This result saw Chiesi Ltd climb further up the all-UK pharmaceutical company league table to attain 17th position (IMS BPI)
Sales progression was largely driven by Fostair, grown of 40% in an extremely competitive environment and its market share continued to grow throughout the period.
Clenil continued to be a key contributor to overall company sales, with a sales achievement in excess of £ 52 million and an increasing market share, now topping 75%.
Contribution from local products remained significant and there are plans to further augment the current range with additional products.
The Special Care Business Unit in particular had a tremendously successful year, producing continued strong results with Curosurf, Bramitob and Peyona.
Plans were consolidated for the company move into the Rare Disease area, with the appointment of a local key account manager to help drive our company's success within this important new business segment.
The affiliate looks forward to the launch of new products across the 3 key business units of Respiratory, Special Care and Rare Diseases.

| United Kingdom | |
|---|---|
| Domestic direct Sales (K€) | 129,875 |
| Variation versus 2012 | 2.4% |
| Human resources | 191 |
| Commercial network | 165 |

# Chiesi Germany

2013 was a very successful year for the German affiliate: direct sales reached € 104 m, up by 6.6%. The Company was able to expand its market share in the German respiratory market (+8%) and reached 4th place among the competitors of this market.
An important event was the launch of Foster Nexthaler in March.
In the first ten months, sales of this new product reached a total of € 9.6 million, which has exceeded expectations by far. Foster continues to represent the biggest share of total revenues with net sales of € 62.7 million. Forair® also performed well and was up by 9.5% on the previous year.
In the field of neonatology Peyona, successfully launched in 2011, achieved sales for € 0.89 m, equivalent to an increase of +7.7%.
The affiliate also successfully implemented iPads for the sales force, using them during the\ meetings as a new means of interactive dialogue with doctors.

| Germany | |
|---|---|
| Domestic direct Sales (K€) | 104,134 |
| Variation versus 2012 | 6.6% |
| Human resources | 204 |
| Commercial network (direct + interim) | 204 |

To support further growth, Chiesi adopted a new organisational model in 2014.
The company is now managed by business units with the fields Primary Care, Special Care, and Business Operations. The aim is to create a more innovative, effective and efficient marketing and sales model.
Two new products will be introduced in the Special Care area this year: an new gene therapy and a product in the kidney and liver transplantation area. They will contribute to further diversify the portfolio.

# Chiesi Central Eastern Europe

The Chiesi Central Eastern Europe Group with its headquarters in Vienna, Austria, is the regional structure representing the Chiesi corporation in the Eastern European Countries (except Poland and Russia) and the countries within the Commonwealth of Independent States (CIS). From Vienna the whole group is serviced in logistics, regulatory, medical and financial matters. Besides Chiesi's corporate products in respiratory disorders, rheumatology and neonatology, the portfolio at regional level is well-established in anaesthesiology, intensive care, rare disease medicines and the treatment of addiction. The Company is actively looking for further in-licensing products for selected business areas.

| Austria & CEE | |
|---|---|
| Sales in Austria & Central Eastern Europe Countries (K€) | 62,535 |
| Variation versus 2012 | 15% |
| Human resources | 177 |
| Commercial network | 88 |

## Chiesi Austria

Chiesi Austria manages the portfolio in Austria with two business units, in Primary and Special Care. The Primary Care unit has a strong focus on respiratory diseases with its flagship Foster as well as an interesting range of products in CNS. The launch of Formoterol MDI and a Montelukast generic further complete the portfolio. The latter unit has a broad product range in intensive care medicine, including Curosurf for premature babies and Bramitob for cystic fibrosis. The in-licensed product Prolastin offers an important treatment for a rare genetic pulmonary disease.

## Chiesi Bulgaria

This affiliate was set up at the beginning of 2008. In addition to Foster and Curosurf, in-licensed Ferriprox (Apopharm, Canada) completes the special care segment. Flamexin was launched in 2006 and is maintaining a strong position among anti-rheumatic treatments.

## Chiesi Czech Republic

The hospital products in particular represent an important basis in the portfolio (Sufentanil, Midazolam, Fentanyl) in the Czech Republic. The respiratory products, especially Foster under the brand Combair, which was launched in 2011, provide great potential for future growth. Bramitob adds to the Special Care product range including Curosurf.

## Chiesi Romania

2013 was still a difficult year for the pharmaceutical industry due to unfavourable changes implemented by the government and a lack of funding for the healthcare system. Chiesi Romania nevertheless managed to develop its position successfully, particularly with Curosurf and Flamexin. Two new launches stimulated the development of the portfolio and the organisation.

## Chiesi Slovakia

The affiliate, which has been operational since 2004, has always achieved considerable success over the years. Since the launch of Foster in 2007, Chiesi has gained a significant market share also at international comparison. In 2013 a formulation containing 180 therapeutic doses was introduced.

## Chiesi Slovenia

The most important areas of activity of this well-established affiliate (since 1998) are in respiratory with Foster and Atimos. ReVia (anti-addiction drug) and Midazolam Torrex are also main contributors to sales in Slovenia.

## Chiesi Hungary

In spite of the difficult pharma-economic situation in Hungary, business was successfully developed, mainly on the basis of sales in respiratory (Foster, Atimos), but also in the anti-rheumatic segment (Brexin) and the affiliate's well-established position in Special and Intensive Care (Curosurf, Bramitob, Midazolam, etc.).

## Chiesi Pharmaceuticals Export Area

The areas managed by the export division are the former Yugoslavian Countries (except Slovenia), the Baltics and the CIS (except Russia, but including Mongolia). Local partners provide registration, marketing and distribution services.
This area currently represents 20% of total revenues for Chiesi Central-Eastern Europe, and is considered a major source of dynamic development for the future.

| Netherlands | |
|---|---|
| Domestic direct Sales (K€) | 23,569 |
| Variation versus 2012 | 55.6% |
| Human resources | 47 |
| Commercial network (direct + interim) | 27 |

# Chiesi Netherlands

It has been a dynamic year for the Dutch affiliate, introducing the Foster MART-indication and Foster Nexthaler. It was again an ambitious year of growth.
With 47 employees the young Dutch affiliate has become one of the 10 biggest contributing country affiliates in terms of revenues within the Group. Revenues are up by 55.6% compared to the previous year and stand at € 23.5 million.
This achievement saw the Dutch affiliate break into the top 32 pharmaceutical companies in Netherlands. The results have been driven by substantial growth rates for the major brands in the respiratory (Foster, Atimos, Bramitob) and neonatal (Curosurf, Peyona) therapeutic areas.
In 2014 the affiliate will leverage on the growth rate of its Primary Care portfolio and continue to focus on strengthening its local presence by expanding its current Special Care portfolio by launching Glybera and Envarsus.
Building the Chiesi brand in Netherlands with corporate social responsibility activities and added-value services and programmes will further enhance the reputation and acceptance of the company and its current and future brands with key players.

| Poland | |
|---|---|
| Domestic direct Sales (K€) | 24,035 |
| Variation versus 2012 | 59% |
| Human resources | 94 |
| Commercial network (direct + interim) | 79 |

# Chiesi Poland

The Polish affiliate, which was established at the beginning of 2005, mainly focusses on developing the position of hospital products: Curosurf and the anaesthetic portfolio. Bramitob has been subsequently added to the Special Care product range. Since 2009 respiratory products, beginning with Budiair and followed by Atimos and Fostex, have boosted the development of the Polish offer.
In 2013 Fostex was the main driver of the affiliate's business, contributing 72.7% to total sales.
In spite of the launch of the first generics on the combo market the Company achieved an excellent performance with a 38.7% growth rate, as the second-fastest growing company in the IMS ranking. This result enabled Chiesi Poland to reach 48$^{th}$ place in the ranking of local pharmaceutical companies and 25$^{th}$ among the innovative companies.

## EMERGING COUNTRIES & INTERNATIONAL COMMERCIAL OPERATIONS

# Chiesi Russia

The Russian market remains one of the fastest-growing pharmaceutical markets, demonstrating +11% growth compared to 2012. Chiesi Russia delivered outstanding results with a +25% growth. Curosurf maintains its leading position in Russia with 95% market share among surfactants; Respiratory portfolio sales continue to grow with the help of the biggest national manufacturer: Pharmstandard.

Although Foster has not been listed in the federal reimbursement system, it was included in 214 territories in the regional reimbursement programmes and achieved sales +34%.

Thanks to the completed market access structure and the cooperation of the field force organization, Curosurf's market share is protected and the respiratory portfolio is more present in the various regions of the territory.

In 2013 the affiliate developed an application for business analysis – the BI System QlikView, usingh the software from the US company QlikTech, and was awarded first prize for the *Best Dashboards* among 35 retail, pharmaceutical and distribution companies.

The main objective for 2014 is to maintain double-digit sales growth. Chiesi Russia continues to focus on the development of Foster and maintain Curosurf's leading position.

| Russia | |
|---|---|
| Domestic direct Sales (K€) | 36,047 |
| Variation versus 2012 | 24.6% |
| Human resources | 103 |
| Commercial network (direct + interim) | 74 |

# Chiesi Mexico

After its first year of successful operations with both Curosurf and Peyona, Chiesi Mexico has been granted authorisation to market directly its products from local regulatory authorities, a regulatory milestone which will give the Chiesi Group 100% control of its operations in Mexico.

The approval of Innovair (Foster) has paved the way for the launch of the respiratory portfolio, which is expected to begin its first local sales from July 2014.

Curosurf achieved double-digit growth in 2013 and Peyona's first year went beyond expectations to become the top caffeine citrate of the Country.

| Messico | |
|---|---|
| Domestic direct Sales (K€) | 6,836 |
| Variation versus 2012 | 79% |
| Human resources | 25 |
| Commercial network | 15 |

| Brazil | |
|---|---|
| Domestic direct Sales (K€) | 63,019 |
| Variation versus 2012 | -1.2% |
| Human resources | 295 |
| Commercial network | 130 |

Mexico is the 15th most important pharmaceutical market in the world and second in Latin America, with an estimated value of $ 14 bn USD.

# Chiesi Brazil

The affiliate achieved an excellent performance in 2013, outperforming the Brazilian pharmaceutical retail market. According to the IMS, the Brazilian pharma market grew by 16%, reaching R$ 57 bn and showing a continuously strong growth trend. In the same period Chiesi Brazil went beyond market levels to achieve a growth rate of 29% in local currency and gain 47th position in the ethical market. Unfortunately, the sharp devaluation of the Brazilian real has much affected the results in Euro.

The affiliate's most recent launch, Fostair pMDI, showed the highest sales growth rate (+43%) out of all the products in its market segment.

Another important achievement is the market penetration of Clenil HFA, now part of the "Farmacia Popular" programme, a programme where asthma sufferers are entitled to a reimbursement of the drug from the government. Clenil HFA grew 210% to become the most prescribed corticosteroid within the FP programme.

The other important products, including Clenil A, Manivasc, Forten, Bamifix, showed good growth in demand .

In October 2013 the Santana de Parnaíba plant passed an AIFA inspection, obtaining the renewal of the GMP certificate and thus ensuring possibility to keep on the supply of Foster pMDI to the EU Countries, for which it is the back-up production site.

The affiliate's main target for 2014 is to continue improving the opportunity of the Brazilian pharmaceutical market growth trend, increasing market penetration with the aim of maintaining growth above market levels. The launch of Fostair NextHaler, which is scheduled for September, has a key role in achieving this ambitious objective. Chiesi Brazil plans to continue increasing local production at the Santana site to support domestic sales growth and increase exports to other Group affiliates.

# Chiesi Pakistan

2013 was a difficult year because of the fight against terrorism, which seriously affected Pakistan's whole economy. In spite of this Chiesi Pakistan achieved 21% growth in local currency. As reported by the IMS the overall company position was 38th, securing a 0.66% market share. These results were due to the efforts of the marketing management and field force who worked in conditions rendered difficult by poor law and order.

The Company reached the objectives set for 2013 as a result of the trust and ethical image Chiesi Pakistan is enjoying within the professional healthcare community.

Developing in line with local market growth trends, Chiesi Pakistan worked dynamically to safeguard the leadership of its flagship products. Foster played a pivotal role in generating these brilliant sale results and it has further strengthened the respiratory line products.

Other corporate product leadership was successfully maintained with significant growth rates, such as those achieved by Atem, Clenil Compositum Aerosol, Clenil Aerosol, and Brexin. Branded generics Pulmikast, Esta, and Esotone also recorded excellent performance.

Curosurf grew of 53% thanks to a dedicated rep line set up for its promotion.

Chiesi Pakistan has set itself ambitious objectives for 2014 with plans to take every opportunity to develop and sustain the affiliate.

| Pakistan | |
|---|---|
| Domestic direct Sales (K€) | 11,677 |
| Variation versus 2012 | 7.8% |
| Human resources | 165 |
| Commercial network | 130 |

# Chiesi Turkey

Despite the downtrend in the market, Chiesi Turkey continued to move decisively towards its goals, achieving 17% sales growth in local currency. Unfortunately, the sharp devaluation of the Turkish lira has much affected the results in Euro.

Throughout the year, various project teams worked extensively in business areas such as Performance Management, Event Management and Customer Relationship Management to improve operational effectiveness.

Foster has succeeded in becoming the fastest-growing product with 13% unit growth, and currently ranks among the top 5 in a highly competitive and crowded

| Turkey | |
|---|---|
| Domestic direct Sales (K€) | 25,602 |
| Variation versus 2012 | -1.5% |
| Human resources | 147 |
| Commercial network | 116 |

market. Rinoclenil also achieved a remarkable 22% unit growth in a declining market and occupied the most prescribed product position in the sector. The growth trend for Foster is expected to continue through the launch of the MART indication in asthma.
Curosurf reached a 70% market share in the surfactant market. In 2014, the launch of Peyona is expected to further enhance Chiesi's reputation in the neonatology field.
Cyladol co-branding with Biofarma will enable us to maximise product potential by increased coverage and frequency in the GP segment. Our primary focus will be in the Business Development area, where various opportunities are being investigated.
The Foster Nexthaler registration file was submitted to boost the life cycle management of the product in Turkey.

# Chiesi China

The Chinese pharmaceutical market continued to perform positively in 2013 (+14% vs. 2012) but the growth rate experienced a significant slowdown compared to the previous year. This was mainly due to the introduction of several price cuts which have also affected Curosurf, the core product of the affiliate.
2013 was a very important year for Chiesi in China for a number of reasons:

- the China Food and Drug Administration (CFDA) granted marketing authorisations for Peyona, Foster and Clenil UDV and their commercialisation began in the 2nd half of the year;
- the joint venture with Eddingpharm became operative with the launches of Foster and Clenil UDV;
- Chiesi China has also improved its marketing strategy by reinforcing educational programmes and its presence at influential congresses including the National Neonatology Annual Meeting, and hosting the Chiesi China Expert Meeting with an attendance of over 100 neonatologists;
- the organisation has been strengthened by introducing new professional figures to sustain company growth in a competitive market.

| China | |
|---|---|
| Primary Sales (K€) | 26,714 |
| Variation versus 2012 | 27.4% |
| Human resources | 89 |
| Commercial network | 68 |

Three Regions have been created with new positions including regional sales managers and local marketing specialists with the aim of improving support for the sales force and optimising the implementation of marketing programmes.

The workforce has been reinforced with the addition of a training manager and new recruits in the Commercial, Finance, Governmental Affairs, Marketing, Medical Affairs, Regulatory Affairs Departments and Sales Organisation functions.

- A new Customer Relationship Management system has been selected with advanced electronic devices for the sales force.
- New offices in Shanghai, Beijing and Guangzhou have become the regional headquarters of the Company employing their own staff for commercial activities and relations with local authorities.
- A more ambitious programme to speed up the registration of new products from the Corporate pipeline has been initiated.

Chiesi China's target for the future is to achieve a stronger growth for Curosurf, as well as to successfully manage the recently-launched products Foster, Clenil UDV and Peyona, and identify new opportunities for business development and continuously upgrade this young organisation.

# Chiesi Pharma Usa

The US affiliate, Chiesi Pharmaceuticals Inc., provides both local and global product development for the Group. The company headquarters are in Rockville, MD, not far from the headquarters of the US Food and Drug Administration (FDA).
In 2013, the Phase 2 clinical study for CHF 5074, a potential new drug for the treatment of Alzheimer's disease, was completed. In addition, the Company continues to be responsible for the implementation of the global clinical programme for the tobramycin project, and provides support for special care and neonatology projects being developed for the US market.

# Cornerstone Therapeutics (USA)

As a specialty pharmaceutical company focused on commercialising products for the hospital and adjacent specialty markets, the Company is actively seeking to expand its portfolio of products for these markets through the acquisition of companies and products and internal development.
Cornerstone Therapeutics is working to advance the following development-stage products to commercialisation:

- Reteplase for IV catheters, an investigational recombinant plasminogen activator for the restoration of function of intravenous catheter devices;

| Usa (Cornerstone Therapeutics. Inc.) | |
|---|---|
| Domestic direct Sales (K€) | 143,918 |
| Variation versus 2012 | 57.4% |
| Human resources | 124 |
| Commercial network | 60 |

- LIXAR (lixivaptan), an investigational, oral selective vasopressin V2-receptor antagonist targeting the treatment of hyponatremia.

In 2013, two products were launched, indicated for some conditions affecting patients with cystic fibrosis: Pertzye (pancrelipase) for exocrine pancreatic insufficiency and Bethkis (tobramycin solution for inhalation), for the management of patients with *Pseudomonas aeruginosa*. To support these launches the sales network was expanded by about 20%.
In September, an antitussive/antihistamine combination product was launched and it is currently distributed by Aristos; this association is the equivalent of the product sold under the Tussionex brand name.
Lastly, the Medical Affairs and drug development teams were expanded to support currently marketed products and increase our focus on the Retavase re-launch; once approved, it will enable the affiliate to further strengthen its relationships with the cardiology community.
The affiliate is focused on the following priorities during 2014:

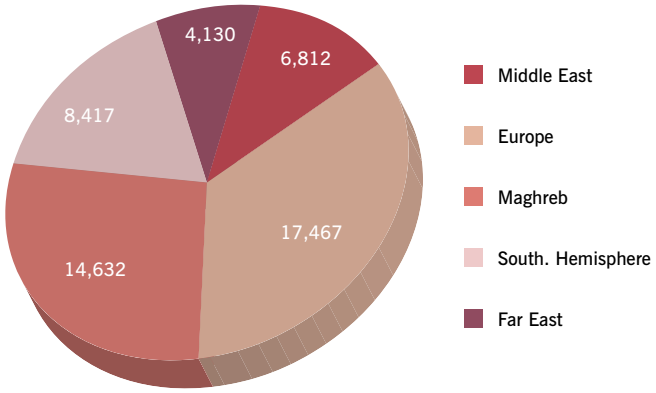
- growing revenue from the existing product portfolio;
- progressing toward validation of a new active pharmaceutical ingredient, or API, supplier and certain manufacturing process changes to allow for the re-launch of Retavase;
- advancing the clinical development programme for intravenous catheters clearance;
- acquiring products in the hospital and adjacent specialty markets.

# International Commercial Operations

In 2013 International Commercial Operations continued to expand the presence of Chiesi products throughout the world in cooperation with its network of established partners, as well as working to expand the Group direct presence in selected markets.
In particular ICO concluded the move to further develop the business in China both by the local affiliate and through a joint venture agreement with Eddingpharm, a Chinese company strongly focussed on the commercialisation of pharmaceutical products. In July 2013 the Chinese operations left ICO and are now directly managed by the Emerging Markets Region.

At the end of of the year an affiliate in the Nordic countries was established, based in Stockholm, with the acquisition of the local company that launched Foster under the brands Innovair in Sweden and Finland and Inuxair in Norway. Chiesi Nordics, with a lean organisational structure and a strong focus on the marketing of Corporate products in the respiratory and neonatology lines, will also launch the products of the Rare-disease franchise recently acquired by the group. In 2014 Denmark will be added to Chiesi Nordics to establish a direct presence in the whole Scandinavian area.
With the support of its Regulatory Affairs Team, ICO continued to succeed in the marketing of Chiesi Corporate products in new areas. In particular 2013 saw the launch of Foster in Saudi Arabia, Hong Kong and Thailand, Curosurf in the Philippines and Peyona in South Korea, Colombia and Malaysia.

ICO revenues by geographic area (€/000)




To be highlighted are the achievements in Tunisia where, through a direct sales force, a growth rate of 14.4% was achieved.
ICO revenues reached € 51.5 m, with the biggest growth coming from the Southern Hemisphere (+12%) and the Middle East (+8.6%). In absolute values, Maghreb and Europe are the main contributors to ICO revenues.
In the ICO portfolio, Curosurf remains the biggest contributor, with a total turnover of € 14.9 m; Foster contributed € 5.7 m and Brexin (PBCD) € 6.3 m.
ICO also continues to commercialise local portfolios through its strategic alliance with strong local partners, and this is especially visible in Algeria, Tunisia and Morocco.

The outlook is positive, with a number of important launches planned in 2014 in existing territories, as well as the opening of new markets through strong collaboration with new partners, continued investment in the development of expertise in the Corporate portfolio via local workshops and the presence at major international congresses throughout the world.

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# SOCIAL RESPONSIBILITY

CORPORATE SOCIAL RESPONSIBILITY ACCORDING TO CHIESI GROUP

BUSINESS ETHICS & GOVERNANCE MODELS

ENVIRONMENTAL CARE & SAFETY

OTHER CORPORATE SOCIAL RESPONSIBILITY INITIATIVE

ADDED VALUE DISTRIBUTION

THE CHIESI FOUNDATION

# Corporate Social Responsibility according to Chiesi Group

The Chiesi Group ensures that the sustainable growth of the business corresponds proportionally to the increase in social commitment, which centres on the person whilst also respecting its values and identity. This commitment is expressed through environmental protection and safety programmes and numerous initiatives which staff at both the head office and the affiliates have set up for the benefit of employees, certain patient groups and local communities. These initiatives demonstrate the ability to exploit the available resources to the full and help those in greatest need and encourage people to take care of their health and the environment. Their geographic location, which extends across four continents, underlines the way in which Corporate Social Responsibility is perceived throughout the all the companies of the Group.
An analysis of added value distribution indicates where the resources produced end up. One particularly interesting figure concerns the investment of more than € 10 million made by the company in 2013 to train its staff. Resources used in this way provide professional and organisational skills which develop individual professionalism and enhance the company's development potential.
The numerous activities run by the Chiesi Foundation are dealt with extensively in the final chapter and underline the Group's commitment to scientific research, training young researchers and international cooperation to promote the exchange of medical and technological knowledge.
The common factor in all these activities is seizing every opportunity to interact constructively with all of the stakeholders, providing them with the Group's knowledge and resources, which are proving to be increasingly useful for protecting the environment, improving social relations and expanding the Group's knowledge.

# Business Ethics & Governance Models

As the Group develops, the level of complexity of its business is ever higher. This means that the areas to which business ethics apply continue to multiply and diversify.
Chiesi already adopted an Ethical Code of Conduct in 2002, with the aim of providing itself with a way to define the commitments and responsibilities needed to carry out the company's activities.
Since then the focus on this issue has continued to develop.

## How this works

The concepts and regulatory standards relating to the practices adopted to manage business ethics are periodically reviewed. In particular, the procedure carried out to achieve this involves:

- benchmarking with regard to regulatory and best practice panoramas;
- a strong emphasis on prevention by means of a system of governance for the whole Group;
- collaboration, involvement and, where necessary, support for the affiliates in correctly interpreting and implementing the Corporate regulations.

In addition, in the countries which have adopted anti-corruption legislation, non-compliance risk assessment activities are carried out with the help of expert consultants together with the local management.

## 2013 Activities

Chiesi has continued to maintain its commitment to these areas whilst also involving the various geographical locations in which it works.
In particular, the monitoring systems of the Ethics & Compliance Guidelines has demonstrated that implementation is almost fully complete, having been extended to Poland and Russia.
The Corporate Compliance Committee has the task of providing the affiliates with support in correctly interpreting and adopting the guidelines and monitoring their implementation.
Over the course of the year the Pakistani and Chinese affiliates were the subject of a General Overview analysis programme. An audit was carried out on the especially delicate processes at the Turkish affiliate.
As far as Italy is concerned, the update of the organisation, management and control Model (based on law 231/2001) has been completed in order to reflect various legal changes (corruption between private parties) and to recognise some organisational, management and governance changes.

## 2014 Programmes

The programme extending the Ethics and Compliance Guidelines to foreign affiliates will also cover Mexico, and the affiliates in Austria, Hungary, Romenia, and Greece.
In Italy an e-learning system about the organisation, management and control Model (based on law 231/2011) will be implemented with the aim of increasing levels of knowledge, dissemination and application.

# Environmental Care & Safety

Aware of the need for sustainable development, Chiesi aims to ensure that its environment and safety performance is carefully monitored and constantly improved.

## Management Systems

At Chiesi the application of the Environmental and Safety Management Systems is a key element to demonstrate to all stakeholders the level of attention it dedicates to people's health, respect for the environment and the controlled use of resources.
In 2012, Chiesi obtained the Environmental Management System certification in accordance with ISO 14001, and the following year concentrated on the integrated management of environmental and safety issues.
The safety regulations are more structured and well known at all levels of the organisation, and there is also a high level of focus on the ethical elements of the environmental regulations and compliance with ecological issues.
The process of continuous improvement has in fact been applied in a similar way to the two systems and is aimed at fine-tuning operative practices and reducing environmental impact.
The Certiquality check carried out in 2013 when the three-year Safety certificate (OHSAS 18001) expired was integrated with the ISO 14001 system.

## Environmental and safety data

The following information provides a summary of the results achieved in the Environmental and Safety performance and the objectives reached in 2013.
It is important to highlight that these objectives were also reached as a result of the careful planning of the new production sites in Italy and worldwide (e.g. DPI in France, Curosurf in Parma, liquids in Brazil). Evaluations of Compliance analysis, Risk Assessment, FMEA and HAZOP were made in 2013 and these will be perfected this year to ensure that the relevant laws are respected and that the best technologies available are used.

# The Environment

Chiesi continues to maintain its commitment to the environmental management programmes aimed at combining the continued growth of production volumes with the careful management of resources used (see tables below for detailed information).

### Energy

The data below demonstrates how the investments made in the past five years have resulted in a drop in energy consumption despite a continuous increase in the units produced. This is an important achievement if we take into account the ever-increasing level of automation, the numerous checks required and above all the

| MAIN PROGRAMMES FOR ENVIRONMENT AND SAFETY IN 2014 | |
|---|---|
| **PROGRAMMES** | **OBJECTIVES** |
| **Extend the BBS method** | The BBS method will be extended to all the operative activities at the San Leonardo site |
| **Reduce water consumption at the research Centre** | Application of the plan drawn up in 2013. The improvement will concern both cleaning activities and the introduction of technological changes |
| **Waste disposal auditing** | Application of the audit plan required for waste disposal firms |
| **New DPI system in Blois** | The new DPI system will be introduced taking mandatory requirements and environmental and safety best practices into account. For this reason the local Health Safety and Environment function will be reinforced by an HSE specialist. |
| **Fire prevention system in San Paolo** | The system, which was designed and set up in 2013, will be completed and implemented to be fully operative in 2014. |

more frequent use of air treatment systems to guarantee the quality of the working environment.
Specific energy programmes have been developed at the Brazilian site through work done on roofing and implementing energy saving programmes during periods when machinery has a lower usage.

## Waste

The slight increase in the production of waste in 2013 is partly due to increased production, the introduction of new processes and also to the removal and disposal of tanks buried underground containing fuel oil, which are no longer in use.
During the year the company's policy also succeeded in ensuring higher levels of recycled waste. In particular, a specific improvement programme was implemented at the French site in Blois aimed at increasing paper and plastic packaging recycling, while in Parma a new ecological area was set up at the San Leonardo plant and an audit programme for waste disposal firms was started up.

## $CO_2$ Emissions

Chiesi's area of production does not generate significant levels of atmospheric emissions. The main source generating emissions are methane boilers.
Throughout 2013 there was a slight increase in these values due in particular to the new Research Centre.

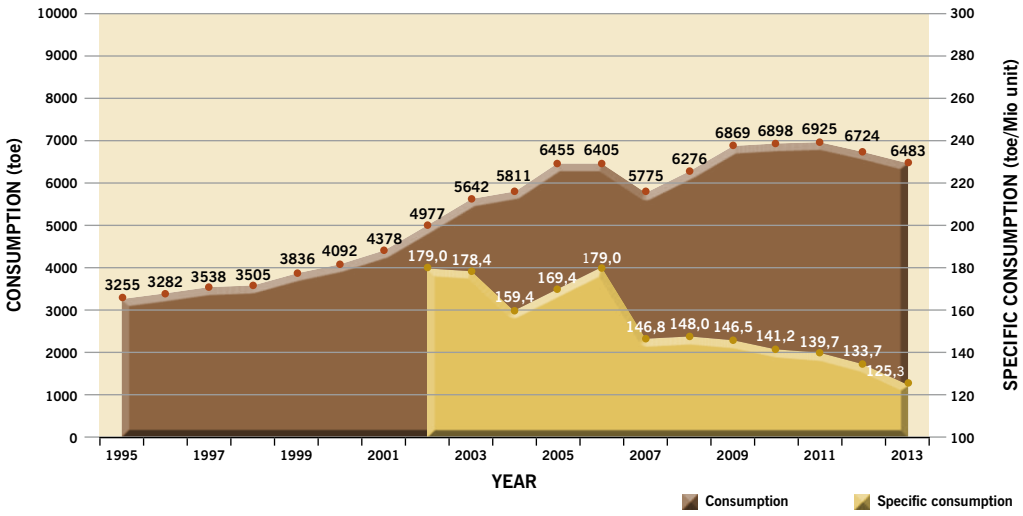
## Water consumption

Figures for water supply and discharge have decreased. The programme run at the Research Centre aimed at studying ways to save water was of key importance.
The analysis highlighted some areas for improvement to implement in 2014.

# Safety

2013 was a positive year for the Group's safety at work figures. The figures have improved significantly both in terms of frequency and seriousness of accidents (evaluated on the basis of days off work).
In order to maintain these results and enhance the Group's performance, a series of improvement programmes have been implemented at all the sites involving an increase in the number of hours of training and other activities aimed at managing specific risks.
Here are some of the most important examples:

Energy indices for the Parma plants




## Extension of the BBSs method

Like a number of other industrial companies, Chiesi has introduced programmes for the application of the BBS (Behaviour Based Safety) method at the via San Leonardo site in Parma. Initially aimed at some of the production areas, the system was then extended to the maintenance area and to the remaining production areas in the course of 2014.

## The application of the State-Region agreement for training

The new legal provision relating to safety training, which has been valid since 2012, provided for complete compliance by the end of July 2013. Chiesi used this requirement as a basis from which to improve the provision of internal training. A further interesting aspect is that since 2013 all members of the Sales Force have taken a safe driving course at the Quattroruote training centre.

## A new procedure for New Chemical Entities management

A new procedure formalises the periodical assessment process concerning toxicological pharmacological information generated by experimental trials on new molecules in conjunction with the Key Stages or Development Gates for each project.

## The new fire prevention system at the San Paolo site

The Brazilian site in San Paolo upgraded its internal fire prevention system with the construction of a new ring, a new 550 $m^3$ water reserve, two 200 CV diesel pumps (one is a reserve for the other) and has optimised the network for detecting and extinguishing fires.

| ASPECT | | 2012 | 2013 | TREND | NOTE |
|---|---|---|---|---|---|
| Internal production | milion units | 63 | 64 | ↑ | **Product**<br>The production trend shows continuous growth. |
| Energy consumption (methane, elettricity etc.) | TOE(*) | 10,679 | 10,549 | ↓ | **Energy consumption**<br>The improvements made over the year and the solutions adopted have resulted in reduced consumption compared to an increase in the number of units. Specific programmes have been developed in Brazil concerning the plan's roofing and energy saving programmes have been introduced. At the sites in France and Parma particular attention will be paid to this aspect when new plant equipment is introduced. |
| Water consumption | $m^3$ | 253,464 | 243,087 | ↓ | **Water Consumption**<br>Levels are decreasing. In 2014, improvement programmes created for the Research Centre in 2013 will be implemented. |
| $CO_2$ Air Emission (from steam generators) | ton | 6,797 | 7,066 | ↑ | **$CO_2$ Emission**<br>Levels had slightly increased. In 2013 new departements/activities have begun at the Research Centre. |
| Waste (total ammount) | kg | 1,769,853 | 1,888,214 | ↑ | **Waste**<br>The increase is due both to the higher number of units produced and new types of waste generated, and to removal and disposal operations concerning undergorund tanks. The quantity of waste destined for recycling has also increased as a result of specific improvement initiatives. |
| Hazardous waste | kg | 214,903 | 291,370 | ↑ | |
| Recycled waste | kg | 821,870 | 911,924 | ↑ | |
| Wastewater | $m^3$ | 170,778 | 146,559 | ↓ | **Water discharge**<br>This figure is decreasing. |
| Work related accidents with absence | n° | 16 | 12 | ↓ | **Work-related accidents**<br>The frequency index (number of work-related accidents) and the seriousness index (lost workdays) are decreasing. Specific programmes are being planned for the various sites to maintain/improve the levels of safety reached. |
| Number of lost workdays due to injuries | days | 218 | 115 | ↓ | |

*The table demonstrates how the efforts made to save energy over the years have resulted in optimal consumption for each unit produced.*

** Tonnes of oil equivalent.*

# Other Corporate Social Responsibility Initiatives

## Pharmaceutical Division Italy

Commitment to improving independent scientific research also continued last year, with the aim of gaining a deeper knowledge within the scope of specific diseases and in particular rare diseases.
This commitment was put into practice with a number of projects, the most important of which are outlined below.
In the rare disease area, focus has been made on neonatology and haematology

- for neonatology, by means of a contribution for the assessment and improvement of the quality of hospital treatments provided for pre-term births and their impact on quality of life, also taking into account healthcare resource consumption;
- for haemoglobinopathies with a contribution for the MIOT project (Myocardial Iron Overload in Thalassemia) run by the CNR (National Research Council) in Pisa, which is evaluating a standardised procedure to monitor hepatic and cardiac iron overload in patients suffering from thalassemia. In the same field, Chiesi also made a significant contribution to the scientific research carried out at the no-profit Franco and Piera Cutino Foundation in Trapani.

In the respiratory area, efforts have been focussed on the GEIRD study (The gene-environment interactions in respiratory diseases project), whose aim is to assess the role of oxidative stress, environmental exposure (pollution, active and passive smoking), diet and genes on the development and persistence of asthma, rhinitis and COPD. The study will generate a database and standardised biobanks relating to respiratory phenotypes and the possibility of sharing the database and gaining access to information on around 4,500 subjects in the 9 Italian centres involved.
A commitment to improving the treatment and quality of life of patients also continued with projects aimed at cystic fibrosis, tardive dyskinesia and osteoarticular diseases.

- As part of a joint initiative with the Italian Centres for Cystic Fibrosis, a home-help programme has been set up involving 6 centres and around 120

patients to provide support to improve therapeutic compliance.

- In the neuropsychiatric field we have supported training events organised by the SIP, SOPSI, DISMOV-SIN, LIMPE and SINC Scientific Societies, in order to enhance close collaboration between psychiatrists and neurologists for the management of tardive dyskinesia, a disorder characterised by a disorder of the body's movements representing serious limitations to daily activities and a severe impact on the social life of psychiatric patients.
- Under the patronage of the FEDIOS (Italian Federation for Osteoporosis and Bone diseases), we have supported the screening of 270 people over the age of 50, with the aim of maintaining osteoarticular wellbeing, with the help of a specialist consultant and the use of instruments and tests to assess risk factors.

**Rare Disease Day**

Commitment to this sector is ongoing through the internal communication campaigns set up for the Day dedicated to Rare Diseases.

## Spain

2013 was an positive year for CSR activities at Chiesi Spain. In line with the company's initiatives, the affiliate has increased its commitment to social welfare creating an internal commission which has proposed various CSR activities based on business ethics principles, the development of people and respect for the social context.
To ensure the development and involvement of the affiliate's people, a team of volunteers from different areas within the organisation has been created, whose task is to promote and implement various actions including:

- the provision of a lorry load of food to a local association of people at a high risk of social exclusion;
- the collection of plastic bottle lids to buy a wheelchairs for children with rare diseases;
- the donation of second-hand clothes for an association whose aim is to integrate socially excluded people and find them a job;
- a food bank for a local association which receives food from the European Federation of the Aliments Bank (FEBA), helping more than 300 families a month.

The latest initiative was a toy collection for a local association which distributed Christmas presents to more than 250 children.

In the same period Chiesi Spain both worked alongside various no-profit organisations employing disabled people and NGOs to improve living conditions and health. As in previous years, the Company worked with Olivera, a cooperative of disabled people, buying Christmas baskets, and with FEMAREC, a foundation for the social, occupational and cultural integration of people at high risk of exclusion.
Over the next few years the Company intends to increase its social commitment by promoting CSR among all those working at the affiliate.

## Greece

In 2013 Chiesi Greece once again continued to implement Chiesi's CSR values in the following areas:

**Support for patients:**

- as the crisis now affects almost everyone in the country, Chiesi Greece is increasing its support for no-profit organisations, such as volunteer-run social retail pharmacies and territorial clinics, by donating more than 18,500 drugs; an initiative supported by the Medical Association in Athens and the Orthodox Church;
- the treatment of a child suffering from cystic fibrosis whose family is unable to fund his medical costs continues to be provided; with the help of the no-profit voluntary organisation "A CHILD'S SMILE", the affiliate has donated all the necessary 2-monthly treatments of Bramitob to the hospital;
- as in previous years, Chiesi Greece sent Christmas gifts to all the children hospitalised at the Centre for Cystic Fibrosis at the Paediatric Clinic, Hippocrates Hospital in Salonika.

**Educational and research support:**

- Chiesi Greece continues to support the Pharmaceutical Department at the University of Athens. The affiliate provided the PhD study grant for two Pharmaceutical Department graduates.

## Germany

Over the past few years Chiesi Germany has already successfully developed a partnership with the comprehensive Geschwister-Scholl school in Hamburg, but in 2013 it was time to set up a new project: helping people from socially disadvantaged families. This objective has been reached by assisting the Bornheide social centre in Hamburg Osdorf.
The centre helps children, teenagers, adults and families, and promotes sport and free time. «Through this project we provide support for integrated health treatment and social services which guarantee rapid assistance for low-income families», explains Kai Joachimsen, Managing Director at Chiesi Germany. Among other services, Bornheide also provides for a service for mothers, a school for parents, an information centre for geriatric care and a club for the elderly. Thirty people from Chiesi Germany have been involved in a series of initiatives including the construction of a tool shed, laying the flooring on a terrace, painting the caretaker's house and cleaning up a refuse container.

## Netherlands

The Clean Air for Everybody Foundation set up in 2012 as an initiative run by the Dutch affiliate has continued to grow and develop. Its objective is to find a solution for the country's air pollution problem and its negative impact on health, by creating a platform for all the public and private parties concerned, i.e. the government, industry, NGOs and the scientific community.
On December 16th 2013 the foundation organised an event about the relationship between air quality and mobility. MPs discussed the topic with scientists, public officials, NGOs, professional organisations, businesses and local and regional governments. By tackling this issue and finding solutions, Chiesi focusses on the activities of prevention of health problems, thus protecting people from atmospheric pollution. In this way, the company will contribute to creating improved quality of life for patients, above all, those with respiratory diseases.
The foundation strengthened its position by involving the Netherlands' former minister for the environment and a former member of the Dutch parliament, as well as two university professors in the Consultancy Committee. The foundation has planned more events with groups of experts in the future.

# Turkey

In 2013 Chiesi Turkey lent its support to two no-profit organisations which help paediatric patients suffering from serious diseases:

- the Leukemic Children's Association;
- the Thalassemic Children's Association.

Working with representatives from both associations, the Company firstly identified their main needs, and then conveyed them internally. Through internal campaigns, the company's staff collected clothes, stationery for school, toys and similar items in order to meet the identified needs and provide psychological support for leukemic children. Help is also given to their families, as many of them have to move to bigger cities in order to access treatment for their sick children.
For the association of children suffering from thalassemia, Chiesi Turkey modernised the room used for daily blood transfusions at the Department of Paediatric Haematology at the University Hospital in Istanbul. The transfusion room was transformed into more suitable environment for these young patients, who have to spend a number of hours there.

# Russia

The 2013 programme to promote CSR among the people working for the affiliate involved the following activities:

- as part of the International Premature Babies Day, Chiesi Russia, with the help of a no-profit organisation, financed the purchase of basic essentials for newborn babies;
- a photographic biennale, held in Moscow as part of the XI International Perinatal Congress, and the "The Breath of New Life" project, aimed at highlighting the mission of neonatologists in preserving the life of their tiny patients.

# Pakistan

For some years Chiesi Pakistan has dedicated its efforts to eradicating tuberculosis through a voluntary organisation known as the Lahore District Anti -TB Association. In addition to making a contribution to the purchase of medicines and equipment, the Company finances a newsletter, published every month in the local language, to raise public awareness about this problem. The newsletter *Naveed-e-Hayat* (Invitation to Life) explains clearly and simply the importance of cleanliness, hygiene and nutrition among ordinary disadvantaged people. Each edition also features an anti-smoking campaign. The Lahore District Anti -TB Association examined more than 25,000 patients during the tax year (July 2012 - June 2013). This is a wide project operating through four clinics in the city of Lahore, that screen patients affected by tuberculosis and provide free testing and medicines.

## USA

In 2013 Chiesi Pharmaceuticals Inc. took part in various initiatives in support of some of the biggest charitable and research and medical development institutes in the US.
The affiliate made a donation to the US National MPS Society and financed research to help develop a cure for mucopolysaccharidoses and related diseases.
In addition, Chiesi Inc. donated to the annual gala evening of the National Organization for Rare Disorders (NORD) to raise funds, the proceeds of which are used to provide support, training and other services to improve the lives of people affected by rare diseases. Further donations were made during the holiday season through a local Holiday Giving Project and the Toys for Tots programme run by the US Marine Corps.Lastly, most of the people at the affiliate were able to benefit from the Chiesi Inc. integration programme, thanks to which donations from the employees were added to by the company up to a certain amount and given to the employees' chosen charitable organisations.

## Brazil

Since 2003 Chiesi has financed a programme run by the Government of the State of San Paolo, called the Programme for the Young Citizen, which extends to the city of San Paolo and also to Santana de Parnaiba. In roughly a decade, the programme has already been able to offer the first job opportunities to a number of young people on low incomes.
Chiesi has also set up a process of responsible waste disposal at the Santana di Parnaiba plant, and thus separating out all recyclable materials. Contaminated and/or infective materials are sent to special containers and then to a company specialising in environmental solutions.

With its field force, Chiesi launched an awareness campaign concerning the replacement of ordinary fuel for cars with ethanol, internationally recognised as an important source of clean and renewable energy. The initiative covered the whole country and is aimed at reducing $CO_2$ emissions.
For the past nine years Chiesi has worked with the Brazilian Association for Leukaemia and Lymphoma (Abrale) and the Brazilian Association for Thalassemia (Abrasta). The funds provided help both organisations in the city of San Paolo to finance treatments for teenagers in particular.

# Added Value Distribution

The added value generated in 2013 shows an overall increase of 25.2%.
In 2013 the costs for services significantly decreased, also due to the evolution of some important clinical trials concluded in 2012, and others that will reach full development in 2014. Nevertheless, R&D expenditure amounted to 13.6% of sales, confirming the importance and strategic value that the Group attaches to this activity. Approximately 50% of the added value is absorbed by the costs and services for staff, which in 2013 went beyond the proportional increase in the workforce. Investment in training continues to represent a key element for the continued development of the Company.

The increase in the Group's margins will help support new initiatives and investments that are essential to the future development of the Group, such as the recent developments at industrial level, the acquisition of Zymenex A/S and the licensing agreement with uniQure BV, a world leader in the research and development of gene therapies.

## Added Value Distribution (Value in Euros/000)

| | 2013 | 2012 |
|---|---|---|
| **Human Resources Return** | **303,804** | **287,288** |
| Wages & salaries, indemnities, other personnel costs | 242,201 | 228,229 |
| Social Security Contribution | 51,266 | 49,511 |
| Training | 10,337 | 9,548 |
| **Public Administration Return** | **106,026** | **65,227** |
| Income taxes | 97,240 | 56,703 |
| Other Taxes net of R&D public grants | 8,786 | 8,524 |
| **Minority Return (Net income to minority)** | **10,232** | **(1,235)** |
| **Company Return (Group Net income)** | **183,752** | **130,971** |
| **Group Added Value** | **603,814** | **482,251** |

# The Chiesi Foundation

Founded in 2005, Chiesi Foundation Onlus is a non-profit organization which seeks to capitalize on Chiesi's legacy of knowledge in order to promote health and alleviate suffering of patients affected by chronic obstructive respiratory diseases, rare diseases and diseases of prematurity.
Chiesi Foundation pursues its mission through research, the sharing of knowledge and by educating healthcare professionals, the public and patients associations.

The Foundation affirms and recognises that its inherent and deeply-rooted values are constituted:

- by the centrality of the human being;
- by the observance of universally accepted ethical principles;
- by the sense of responsibility towards the environment and society;
- by the sharing of science and knowledge without limits or restrictions;
- by the fight against suffering and inequality.

The Chiesi Foundation's main areas of activity are:

- Scientific research to better understand the patients' needs and improve their management, through the study of physio-pathological mechanisms, of phenotypes and in depth analysis of psychological aspects of patients care.
- Diffuse scientific knowledge in order to improve the taking-care of patients and to favor a better understanding of their needs by both the public domain and the institutions.
- Training for young researchers, to promote academic scientific research and contribute to healthcare professions, by financing doctorate research projects.
- International cooperation in sharing medical and technological knowledge and transfer of means to developing countries across long-term projects orientated to self-financing.

Chiesi Foundation is governed by a Management Committee, accountable for the approval of the budget and the plan of activities, and by a Scientific Advisory Board for matters of a scientific nature, made up of outstanding members of the medical community.

# Scientific Research and Dissemination

Chiesi Foundation finances research projects with a high medical-scientific profile and those of particular social interest and is committed to the dissemination of the scientific knowledge they generate.

### Respiration Day

An international event with a high scientific profile which offers doctors and researchers the opportunity to compare and exchange ideas and experiences regarding the latest developments in pulmonology. The aim of this event is to help raise awareness about respiratory diseases and aid in their prevention. The 2013 Respiration Day took place on May 31st at the Paganini Auditorium in Parma and was dedicated to the theme: "*Managing exacerbations of asthma and COPD: are we there yet?*". Over 700 lung specialists from all over the world took part in the event.

### Maurizio Vignola Award on Innovation in Pneumology

An initiative set up jointly with the European Respiratory Society to make scientific research and the development of know-how in the respiratory disease field widely available. The Award, which is dedicated to the memory of Maurizio Vignola, a prominent researcher, each year offers a grant for 20,000 euro to the authors of the most interesting scientific work about the key mechanisms of chronic respiratory diseases. The 2013 edition of the Award was assigned to two young researchers: to Dr. Miguel J. Divo for his work published in 2012 in the American Journal of Respiratory and Critical Care Medicine entitled "*Co-morbidities and risk of mortality in patients with chronic obstructive pulmonary*

*disease*", and to Dr. Firdaus A.A. Mohamed Hoesein, for his work published in 2011 in Thorax with the title "*CT-quantified emphysema in male heavy smokers: association with lung function decline*".

In the field of scientific research, the foundation financed 5 projects in 2013:

- *New therapeutic strategies for the reduction of infant mortality in the Middle East: sustained lung inflation and brain cooling*, Dr. Gazzolo – SS Antonio Biagio and Cesare Arrigo Hospital;
- *Elaboration of a flow chart for the evaluation of the role of the small airways in the phenotypic expression in bronchial asthma*, Dr. Contoli – Ferrara University;
- *Long-term clinical, functional and farmaco-economic phenotypisation of patients with Small Airways Disease (SAD) in asthma*, Prof. Dal Negro – R&CG Srl;
- *New strategies in neonatal resuscitation: biochemical and respiratory effects*, Prof. Lista – "V. Buzzi" Children's Hospital;
- *Stratified genetic approaches in severe asthma*, Prof. Hall – University of Nottingham.

In the field of dissemination of scientific knowledge Chiesi Foundation has collaborated to a publication and sponsored two events:

- "*European Respiratory News*", a scientific publication intended as a source of information on the activities carried out and point of reference for specialists and patients;
- "*Essential treatments for neonates where resources are limited*", a course organised by the Italian Neonatology Group designed for around 30 healthcare workers due to take part in missions in low-income countries;

- "*World COPD Day*", an annual international event which was promoted for the first time by the EV-K2 CNR Committee in Kathmandu in Nepal, as part of the *Breathing Himalaya* project: *Let's learn to breath*, by means of a conference to illustrate the principle guidelines for the diagnosis and treatment of chronic obstructive pulmonary disease (COPD).

The scientific studies which received an unrestricted grant from the Chiesi Foundation, published this year in peer-reviewed journals are the following:

- *Rhinovirus infection causes steroid resistance in airway epithelium through nuclear factor kB and c-Jun N-terminal kinase activation.* Papi et al.(J.Allergy Clin Immunol.);
- *Bronchiectasis and severe respiratory insufficiency associated with a new surfactant protein C mutation.* Cutrera, Danhaive et Al. (Acta Pediatrica);
- *Respiratory Q1 Insufficiency in a Newborn With Congenital Hypothyroidism Due To a New Mutation of TTF-1/NKX2.1 Gene.* Cutrera, Danhaive et Al. (Pediatric Pulmonology);
- *Modulation of the Expression of the Pro-inflammatory IL-8 Gene in Cystic Fibrosis Cells by Extracts Deriving from Olive Mill Waste Water.* Borgatti et Al. (Based Compl.and Alternat.Medicine Volume);
- *Echocardiography, spirometry, and systemic acute-phase inflammatory proteins in smokers with COPD or CHF: an observational study.* Fabbri et Al. (Plos One);
- *Coronary artery disease concomitant with chronic obstructive pulmonary disease.* Fabbri et Al. (Eur J. Clin Invest);
- *Mechanisms of acute exacerbation of respiratory symptoms in chronic obstructive pulmonary disease.* Fabbri et Al. (Eur J.Clin Invest).

## Training and Support for Young Researchers

Chiesi Foundation supports the scientific activities of young researchers by assigning grants to enable them to set up research projects.
In 2013 the foundation supported the international training programme for young Italian Neonatologists, I.O. PhD. The three-year joint initiative involved financing for the completion of an International Research Doctorate with the Cesare Arrigo Hospital in Alessandria and Universities of Utrecht and Maastricht, under the patronage of the SIN (Italian Neonatology Society).

This year we have also continued to support the 3 Research Doctorate projects which are still running:

- *The Role of adrenomedullin in the treatment of respiratory distress syndrome,* Dr. Li Volti – Catania University;
- *Chronic Obstructive Pulmonary Disease (COPD) in smokers: identification of pro-inflammatory molecular markers and anti-inflammatory molecules,* Dr.ssa Borgatti – Ferrara University;
- *Polymorphisms of the adrenergic cholinergic muscarinic receptors in the physiopathology of COPD*, Dr. Pierdonato – Azienda Ospedaliera Sant'Andrea in Rome.

## International Cooperation Projects

International cooperation is a commitment which the Chiesi Foundation fulfils by supporting initiatives aimed at sharing tools and know-how with low-income

countries with a strong focus on the long-term sustainability of the project and its progressive economic independence.

**Centre for maternal and infant health, St. Camille Medical Centre, Ouagadougou – Burkina Faso**

The Chiesi Foundation continues to support this joint initiative with the St. Camille religious order to build a new neonatology ward for the Centre for maternal and infant health in Ouagadougou, Burkina Faso, where around 1,500 critically ill neonates are hospitalised each year.

**Mother-and-child centre, San Giovanni Paolo II Hospital, Bossemptelè – Central African Republic**

Chiesi Foundation has lent its support to the San Giovanni Paolo II and St. Camille Hospitals in Bossemptelè, in the Central African Republic. As a result of the project, an outpatient clinic for maternal and infant health and a paediatric ward were opened and are now fully operative.

**Centre for maternal and infant health, St. Jean de Dieu Hospital, Tanguietà - Benin**

In 2013, the foundation sustained part of the operational costs and expenditures for medical training for staff at the new neonatology ward, which was officially opened 2012, at the St. Jean de Dieu hospital in Tanguietà, Benin, run by the Congregation of the Fatebenefratelli. Most of the funds allocated for this project were raised following a charity event organised jointly by the Chiesi Foundation and Silvano Romani Catering. The charity dinner was attended by over 300 people, and their generosity made it possible to donate 23,000 euro to the neonatology ward to cover around a quarter of the yearly running costs.

**Istituto dei Poveri Servi della Divina Provvidenza, Marituba - Brazil**

This is the Hospital of the Congregation of the Poveri Servi della Divina Prov-

videnza, in Marituba, a suburban centre of Belem, the capital of the Brazilian state of Paraná. For the past few years, the Congregation, as part of a joint initiative with the doctors at the Negrar Sacred Hearts Hospital, is organising a programme of improvements aimed among other things at setting up a Thoracic Endoscopy service at the Hospital of Marituba.

**Maiani Polyclinic – St. Rita Centre, Cuzco – Perù**

Chiesi Foundation continues to support the Augustinian missions through the Apurimac Association, whose name comes from a region of Peru in the heart of the Andes mountains and whose inhabitants live in small centres situated at an altitude of over 3,000 m.

The project has improved the existing healthcare services, developed an integrated training programme intended for medical staff at the polyclinic and enhanced the biodiversity and cultivation techniques of the officinal plants by designing and building a greenhouse.

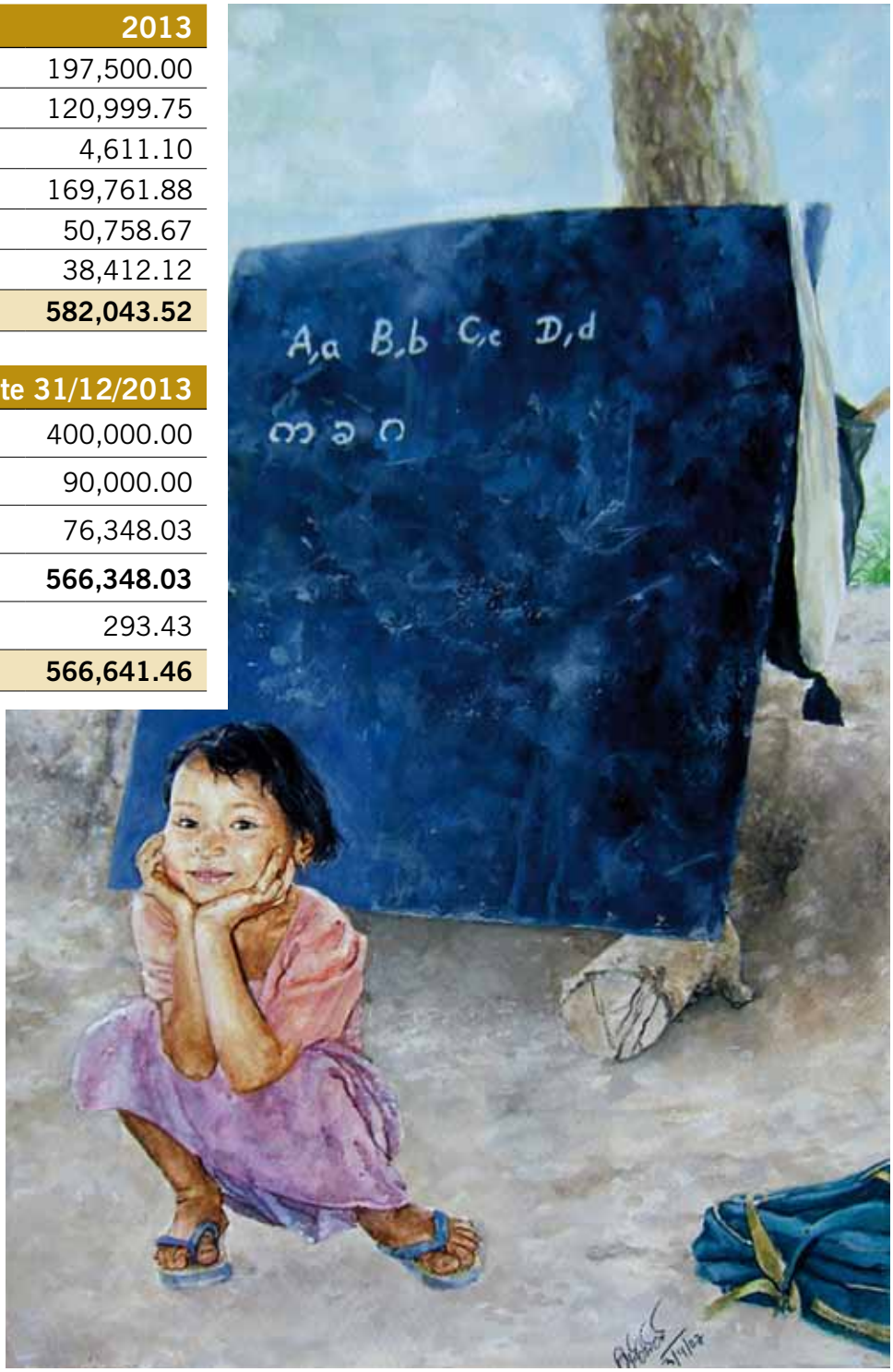
In 2013, the Foundation also supported:

- *Fidenza for Children Onlus*, an association with a project to rebuild the "Casa de los niños", run by the Identes missionary fathers, in San Miguelito in Bolivia.
- The *Burmese Migrant Worker's Education Committee* Organisation to maintain the Nya Li Ha Hta school, which takes in Karen children who are refugees from nearby Burma, in Mae Sot in Thailand.

# Financial Report 2013 (Value in Euro)

| | 2013 |
|---|---|
| Research | 197,500.00 |
| Education | 120,999.75 |
| Communication activities | 4,611.10 |
| Solidarity | 169,761.88 |
| Publications | 50,758.67 |
| Administrative costs | 38,412.12 |
| **(A) TOTAL EXPENDITURE** | **582,043.52** |

| **SOPPORT & DONATIONS Estimate 31/12/2013** | |
|---|---|
| Chiesi Farmaceutici | 400,000.00 |
| Valline | 90,000.00 |
| Other Donations | 76,348.03 |
| **TOTAL INCOME** | **566,348.03** |
| Income from financial operations | 293.43 |
| **TOTAL REVENUES** | **566,641.46** |



# Glossary

**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.

**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):** innovative 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.

**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):** it 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.

**Piroxicam β-cyclodextrin (PBC):** a successful example of "host-guest"

technology, whereby the host, a starch derivative known as β-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.

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

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Chiesi

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