



GONADOTROPINS
PURIFICATION
PROCESS

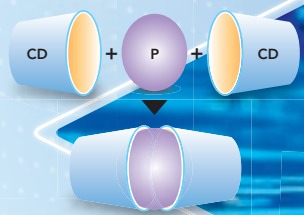
ORODISPERSIBLE
FILMS



SOFTGEL
CAPSULES



PROGESTERONE
& β CYCLODESTRINE



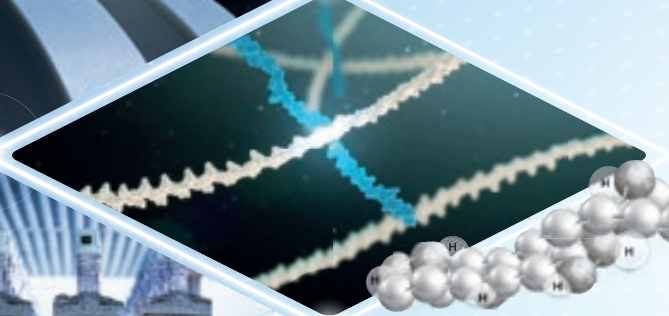
PRE-FILLED
SYRINGES



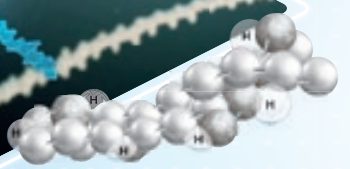
TRANSDERMAL AND
TOPICAL PATCHES



SINGLE
DOSE STRIP



BOV
(BAG-ON-VALVE)



NAHYCO
HYBRID TECHNOLOGY



DEVICE FOR
INTRAVESICAL
INFUSION



Technologies in effective shape



Caring Innovation



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IBSA Institut Biochimique SA

“The road to be travelled in order to transform an idea into a tangible and productive project is research that focuses on real requirements, combined with a vocation for solving the everyday practical issues associated with the needs of both doctors and patients”.

Dr Arturo Licenziati, Founder and CEO of IBSA

We are a multinational pharmaceutical company with a specific vision of care that we project from our headquarters in Switzerland to the rest of the world, through a process of on-going expansion in Europe, Asia and North America.

27 million vials of hormones, 374 million of soft gel capsules, 78 million packs of finished products: this is the productive capacity on which IBSA is building its history. Established in Lugano in 1945, IBSA started developing its special identity in 1985 when it was acquired by the current ownership, which completely overhauled both its vision and its strategy by focusing on the acquisition of technological resources able to improve the quality of existing therapeutic solutions and launching a development programme aimed at consolidating the global expansion strategy and developing company assets. IBSA holds 90 patent families, and others are currently being developed.

The company headquarters are in Lugano (Switzerland), with manufacturing sites and R&D laboratories throughout Switzerland, Italy, France and China.

We are present in over 90 countries in 5 different continents, with 18 subsidiaries, in Europe, China and the United States and employ more than 2,200 collaborators in our headquarters, subsidiaries and manufacturing sites, with a consolidated turnover of 900 million Swiss francs. We also boast an extensive product portfolio covering 10 therapeutic areas and we are one of the major players worldwide in the area of Reproductive Medicine and one of the world leaders in hyaluronic acid-based products.



IBSA in the world

● HEADQUARTERS
Switzerland, Lugano

● SUBSIDIARIES
Austria, Vienna
Belgium, Bruxelles
China, Qingdao and Rizhao
Czechia, Praha
France, Antibes
Germany, Düsseldorf
Hong Kong SAR
Hungary, Budapest
Iberia, Barcelona
Italy, Lodi
Netherlands, Amsterdam
Nordic, Copenhagen
Poland, Warsaw
Slovakia, Bratislava
Switzerland, Lugano
Turkey, Istanbul
UK, London
USA, Parsippany NJ

○ PRODUCTION SITES
Switzerland (6 sites)
Italy (3 sites)
China (2 sites)



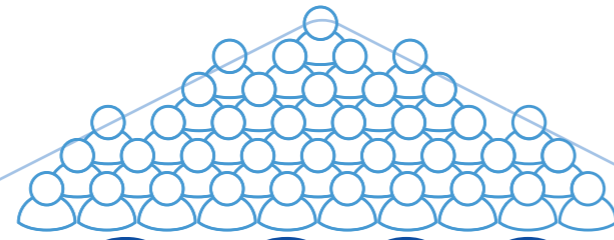


Numbers

PRIVATELY-OWNED
PHARMACEUTICAL
COMPANY
FOUNDED IN

1945 / 1985

ACQUISITION
BY THE CURRENT MANAGEMENT



over

2,200

collaborators worldwide



Operating
in over

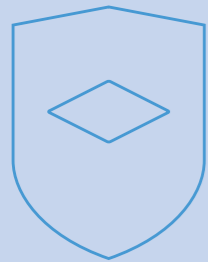
90

COUNTRIES
on 5 continents



MAIN MARKETS

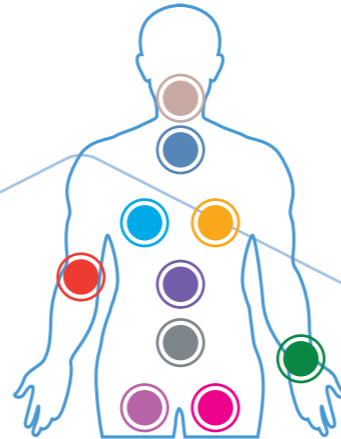
SWITZERLAND, EU, USA,
MIDDLE EAST, FAR EAST AND
NORTH AFRICA



90

patent
families

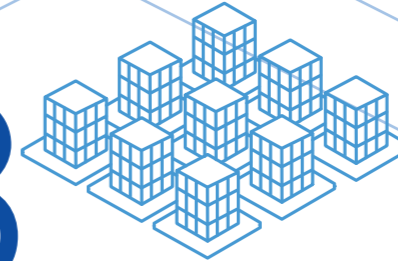
and several others
in the pipeline



10

main therapeutic

AREAS



18

subsidiaries

one of the
MAJOR
PLAYERS
WORLDWIDE IN THE FIELD OF
REPRODUCTIVE
MEDICINE



ONE OF THE
WORLD
LEADERS
IN HYALURONIC
ACID-BASED PRODUCTS



Over

130

collaborators in

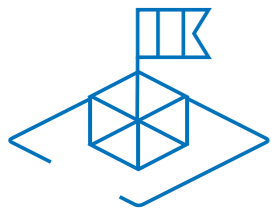
R&D

in Switzerland, Italy,
France and China

27 MILLION
vials of
HORMONES

78 MILLION
PACKAGES
of finished products

374 MILLION
SOFT GEL CAPSULES
produced annually
in our factories



IBSA Italy

As a member of the IBSA Group, our work is based on the **fundamental pillars People, Innovation, Quality and Responsibility** and all company activities are performed in compliance with the principles set forth in the Group's Ethical Code and Anti-bribery Guidelines.

IBSA Italy is a member of the IBSA Group. Established in 1992, the company has a head office in Lodi, **two manufacturing sites** near Milan, three R&D labs, a branch office in Rome, a workforce of over 593 resources and an annual turnover of over 305 million euros. These are just some of the figures that makes us a **scientific economic and industrial leader in the Italian pharmaceutical sector.**

Our production lines are characterised by state-of-the-art technology and environmental sustainability and our Research & Development activities employ **latest-generation technologies** to optimise the bioavailability, efficacy and safety of existing active substances in order to develop simpler, more evolved treatment systems as part of our commitment to provide healthcare professionals with efficacious and reliable novel treatment solutions able to improve patients' quality of life.

The original results of a number of Italian studies, of which many developed in partnership with our universities, are protected by international patent. IBSA holds 90 patent families, and others are currently being developed

We contribute to the success of Italian industry by placing on the market products developed by Italian researchers and manufactured by technical staff and workers in Italy before being sold in 90 countries worldwide.

Our product portfolio covers 10 different therapeutic areas and includes different therapeutic categories, such as prescription drugs, OTC medicines, medical devices and food supplements.

The company's on-going investments in human resources, innovation and productive capacity allow it to maintain a healthy new product pipeline.

As a member of the IBSA Group, our work is based on the **fundamental pillars Person, Innovation, Quality and Responsibility** and all company activities are performed in compliance with the principles set forth in the Group's Ethical Code and Anti-bribery Guidelines, in the firm conviction that an attention to the lawfulness, principles and values they enshrine are essential conditions of company life.

IBSA Italy has established an Organisation, Management and Control System in compliance with Legislative Decree no. 231 of 8 June 2001.

IBSA

IBSA Farmaceutici Italia srl



Business development

Since 2018, there has been a new Department in IBSA fully dedicated to Business Development, Licensing activities and CDMO projects.

Licensing

The Business Development Dept. is constantly looking for partners and international distributors for licensing agreements in countries where IBSA does not operate directly with its branches.

IBSA is focused on strategic collaborations **to achieve a common goal while sharing responsibilities, resources, risks and rewards.**

Close ties with local distributors are crucial for IBSA to grow at an international level.

The Business Development Dept. also evaluates licensing-in opportunities for the expansion of product portfolio.

CDMO

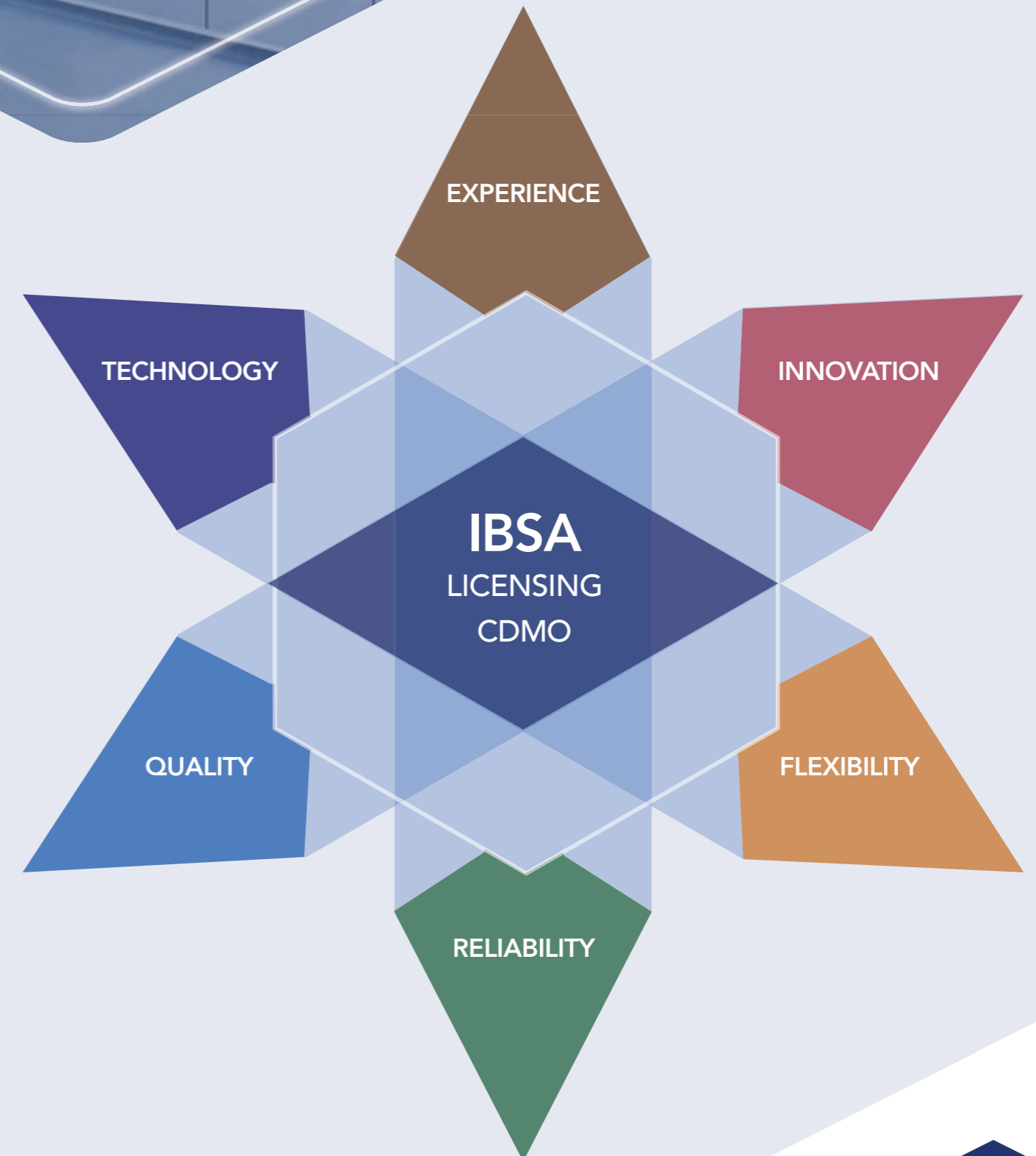
Thanks to its consolidated experience, its industrial capacity and its proprietary technologies, IBSA is **the ideal partner to serve other companies in the pharmaceutical industry**, on a contract basis, **providing comprehensive services** from drug development through drug manufacturing for EU and non-EU markets.

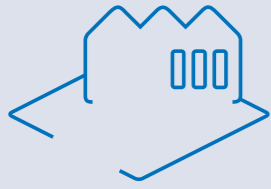
IBSA provides a customized service consisting of:

1. **product concept and pre-formulation**
2. **formulation and process development**
3. **development and validation of the analytical method**
4. **pre-clinical investigation**
5. **pilot and scale batches**
6. **clinical batches**
7. **studies and stability test**
8. **scientific and regulatory assistance**

IBSA has a great experience in all product categories:

1. **drugs:**
 - OTC
 - ethical drugs
2. **medical devices**
3. **nutraceuticals**
4. **cosmetics**





Manufacturing sites

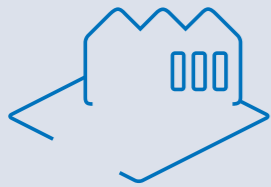
Following its establishment in 1945, IBSA Institut Biochimique SA launched an **extraordinary development programme** aimed at consolidating a global strategy of geographical expansion and developing company assets, which has made it a world market leader in certain specific therapeutic areas, whose products are sold in over 90 countries in 5 different continents.

The headquarters of the IBSA Institut Biochimique SA Group is located in Collina d'Oro just outside Lugano in Switzerland. The Group now consists of 18 subsidiaries in Europe, China and the United States, and boasts a vast product portfolio. We are one of the major players worldwide in the area of Reproductive Medicine and one of the world's leaders in hyaluronic acid-based products.

Over the years, we have grown a great deal also outside Switzerland with over 2,200 collaborators divided between the headquarters, the subsidiaries and manufacturing sites.

Each manufacturing site is dedicated to specific product ranges, in compliance with the separation of productive processes principle: a strategy that has made it possible to obtain certification by the most stringent regulatory authorities, as demonstrated by the recent approval of IBSA products in the United States.





Lamone

The Lamone plant in the Canton of Ticino, Switzerland

The Lamone plant produces gonadotropins and progesterone, hormones used in medically-assisted procreation (MAP) techniques.

More specifically, the gonadotropins (FSH, hMG and hCG) are obtained from donor urine. As the medically-assisted procreation (MAP) area is a demanding challenge for the pharmaceutical sector, we have developed a dedicated plant and patented an exclusive human gonadotropin purification process. The manufacturing process starts in China, with the collection of urine and the production of a processing intermediate known as "crude". **The final phases of the purification process take place at the Lamone plant**, where the hormone range is produced in compliance with the highest purity and safety standards to preserve the integrity of the hormone's glycoprotein structure. **At the end of the purification process the hormone is freeze-dried and packaged.** **We have developed an innovative technology that aims to improve local tolerability** to make the progesterone water-soluble and suitable for delivery by subcutaneous injection.

The Lamone site, where all this takes place, occupies a total surface area of 1,580 m², including the production departments (1,160 m²), warehouse (190 m²), auxiliary areas and plant rooms (230 m²). A total of 354 collaborators work in the Manufacturing department. **This plant represents an example of our strategic choice to develop innovative**

and patient-friendly formulations and produce them entirely in-house. The site therefore accommodates, in a self-sufficient manner and on a single premise, all the various aspects of processing, from purification to the finished product, quality controls and packaging.

The creation of the plant involved hefty investments and required a number of particular design and logistic organisation measures to **meet the highest applicable national and international quality standards.** The considerable investments made over the years have made it possible to **improve the efficiency of the production lines**, which in 2022 produced 27 million vials.

With this state-of-the-art plant, IBSA challenges one of the most complex and stringently-regulated sectors of the pharmaceutical industry, by developing and patenting novel purification techniques.

The hormones produced at the Lamone plant serve the entire IBSA Group and directly supply a number of markets, including, in addition to Italy, Switzerland, Europe, South Africa, South America, the Middle East and Asia.

The plant, considered in the pharmaceutical industry as a centre of excellence, is subject to regular GMP compliance inspections by national and international authorities, including Swissmedic, the ANVISA and the Russian authority. The quality system that governs all plant operations was designed to comply with the various international standards, including both those implemented in Europe (Eudralex, Volume 4) and the US (CFR), as well as the ICH and PIC/S guidelines.

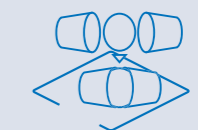
Year	2001
Surface	4,700 mq
Collaborators	104
Therapeutic doses	27 mio/year



Tablets

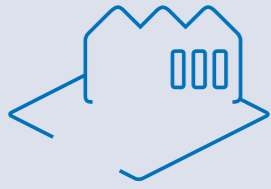


Purification process



Progesterone





Manno

The Manno plant in the Canton of Ticino, Switzerland

The Manno manufacturing site produces thyroid hormones T3 and T4 (liothyronine and levothyroxine), in two pharmaceutical forms: **soft gel capsules** and **liquid oral solutions** in multi-dose and single-dose containers. Soft gel offers the advantages of high dosing precision, greater bioavailability and better stability, while the liquid oral solutions of Levothyroxine are dispensed in single-dose strips that are easy to use even for those with swallowing problems or dysphagia, such as babies and the elderly.

The manufacturing site has a surface area of 3,950 m² and it is composed of five floors of which four are used for production and one is dedicated to the air treatment systems as well as the systems used to produce the fluids required for the conditioning of the production areas:

- floor 1 is home to the first oral solution filling and packaging line, a dispensing area in which all the excipients required for the production operations to be performed in the department are weighed and a material storage and transfer warehouse area;
- on floor 2 of the building, the second liquid oral solution filling and packaging line is located.
- floors 3 and 4 are dedicated to the manufacture of soft capsules: each floor, one the mirror-image of the other, is divided into a bulk area in which the excipients are received and processed to prepare the soft gel (fill and shells) required to form the capsules; from the encapsulation room, the heart of the department, the "fresh" soft gel capsules are transferred to a dynamic and static drying area. Once they have undergone visual inspection by an automated 100% control process using a high-definition video camera system, they are

individually labelled by means of a laser etching system. The last step of the production process is packaging in blisters and secondary packaging for sale. All critical areas are kept under controlled temperature and humidity conditions.

At the current time, the productive cluster is staffed by a total of 166 resources, considering the production facilities, Quality Assurance and Quality Control functions, Technical Maintenance Services and Warehouse Service.

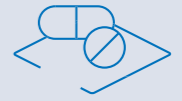
All production steps are monitored by computerised systems that meet the Data Integrity requirements of the highest quality standards.

The soft gel capsules produced at the Manno plant serve the entire IBSA Group and directly supply a number of markets including Switzerland, Europe (Russia excluded) and the United States.

The plant, considered in the pharmaceutical industry as a centre of excellence, is subject to regular GMP compliance inspections by national and international authorities, including Swissmedic, the FDA and the Russian authority.

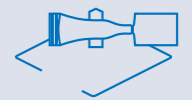
The site is authorised by the local authority Swissmedic, the FDA and the European authorities.

The quality system that governs all plant operations was designed to comply with the various international standards, including both those implemented in Europe (Eudralex, Volume 4) and the US (CFR), as well as the ICH and PIC/S guidelines.



Tablets

Year	2006
Surface	3,900 mq
Collaborators	95
Therapeutic doses	328 mio/year

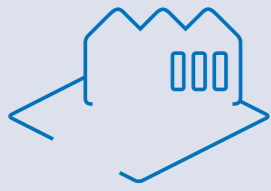


Single dose strip



Soft gel capsules





Collina d'Oro

The Collina d'Oro plant in the Canton of Ticino, Switzerland

The CorPharma plant in Collina d'Oro manufactures and packages **various pharmaceutical forms,**

including syrups, creams and ointments in tubes, oral liquids in stick form, tablets and hard gelatine capsules in blister packs, and granules in sachets, covering a number of therapeutic areas, such as the cosmetic dermatology and osteoarticular, pain and inflammation, respiratory, urology and cardiometabolic areas.

The production Cluster occupies a 3,600 m² site and employs a workforce of 75 collaborators on 13 different production lines. Each year, it manufactures 300 million therapeutic doses. The various products are placed on the market in more than 90 countries worldwide.

The Cluster is inspected regularly by both the national authorities and ISO certification bodies.

The site is authorised by Swissmedic, European authorities and those of the countries where the products are placed on the market.

The quality system that governs all plant operations was designed to comply with the various international standards, including both those implemented in Europe (Eudralex, Volume 4), as well as the ICH and PIC/S guidelines. The quality of both the products and the manufacturing operations is monitored constantly by the Quality Control department and supervised by Quality Assurance.

All operations regarding the manufacture of the bulk medicinal products and their primary and secondary packaging take place on production lines fitted with control and monitoring systems to **guarantee optimum product quality and, therefore, patient safety.**

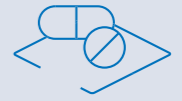
IBSA implements a traceability system for its products

and primary and secondary packaging, involving the application of a barcode and a 2D reading system on an innovative adhesive medium, so that the information cannot be tampered with or modified.

The packaging lines are therefore equipped with serialising systems that ensure consumer protection and safety through a correct management of the labelling of the packing processes and guarantee the reputation of the brand.

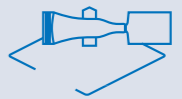
The production of ointments in tubes takes place using starting materials dispensed into BINS that are carried by an automated conveyor system to the vicinity of the production equipment, where a 2000 kg turbo emulsifier connected to 6 tanks directly feeds the 2 filling and secondary packaging lines. The turbo emulsifier, holding tanks and conveyor line are fitted with an automated CIP/SIP system.

The manufacture of syrups involves fitting a cap containing the active substance onto a vial filled with the solvent manufactured and held in tanks connected directly to the filling line and sealed with an aluminium disk. The vial is then labelled and provided with a measuring cup before being placed inside the secondary packaging.

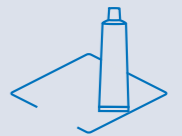


Tablets

Year	1998/2017
Surface	3,600 mq
Collaborators	84
Therapeutic doses	300 mio/year

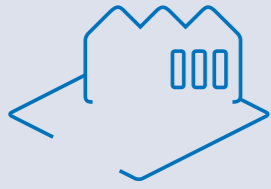


Single dose strip



Tube





Lodi

The Lodi plant, Lombardy, Italy

Over the years, the Lodi plant, which was purchased by the Swiss Group Institute Biochimique SA in 2001, has seen a **complete and radical revamping of the existing production areas**

and the construction of a new state-of-the-art manufacturing facility equipped with cutting-edge production lines for the development of novel delivery systems for medicinal products, medical devices and food supplements.

The plant covers a total surface area of 12,000 m², housing 12 production departments, the warehouse and starting material sampling areas, the dispensing department for the preparation of work orders, the Research & Development labs, the chemistry and microbiology Quality Control labs, and the Regulatory Affairs, Quality Assurance, Production, Engineering and Maintenance offices.

The pharmaceutical production area and the starting materials warehouse occupy 5,500 m², whereas the food supplement manufacturing area and its dedicated warehouse occupy a surface area of 1,000 m².

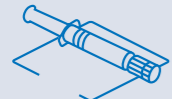
The plant is staffed by a workforce of 224 resources.

The nearby Lodi 2 area is home to the Management Offices and the packaging materials and finished product warehouse. This warehouse is currently being extended and once the construction work is complete it will occupy an area of over 2,500 m².

The plant manufactures products for injection, both in sterile conditions and terminally sterilised, in **conventional ampoules and pre-filled syringes, preparations for topical use** (creams, gels and solutions) in BoV (Bags on valves) **and soft capsules** (soft gel).

The plant's production lines boast **state-of-the-art technology** Insert and are **environmentally sustainable**.

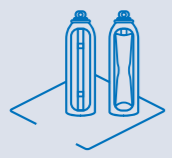
The hefty investments made for the modernisation of the industrial plant and processing lines have made it possible to achieve production plants with high efficiency standards.



Pre-filled syringes



Soft capsules



BOV

The annual production capacity of the various product ranges is as follows:

• Conventional ampoules	12 million units
• Pressurised cans (BOV)	7.5 million units
• Aluminium tubes	2 million units
• Pre-filled syringes	20 million units
• Soft capsules - pharma line	160 million units
• Soft capsules - nutraceutical line	135 million units

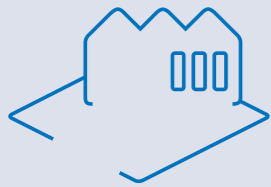
Year	2001
Surface	12,000 mq
Collaborators	224
Therapeutic doses	300 mio/year

The pharmaceutical products manufactured at the Lodi 1 plant serve the IBSA group and supply a number of markets including, in addition to Italy, Switzerland, Great Britain, Hungary, Slovakia, Czech Republic, Poland, Greece, Spain, Scandinavian countries, Russia, Egypt, Turkey, United Arab Emirates, USA, Brazil and Korea.

AUTHORISATIONS

- Italian Medicines Agency (AIFA) (for the pharmaceutical products mentioned - two-yearly inspections)
- GMP Certificate
- FDA Certificate (for certain specific products)
- Quality System: Certified in accordance with ISO 9001: 2015 and ISO 13485 2016 (IMQ)
- Manufacture of Medical Devices: subject to regular inspections by the various European Notified Bodies
- Manufacture of nutraceuticals: authorised by the Ministry of Health and supervised by the Local Health Service.





Cassina de' Pecchi

The Cassina de' Pecchi plant, Lombardy, Italy

The Cassina De' Pecchi plant, which was founded in 1994 and purchased by IBSA in 2010, boasts **20 years' experience in the production of patches containing diclofenac, fentanyl, nitro-glycerine and piroxicam.**

In 2017, it started manufacturing **sildenafil in orodispersible film (ODF)** and in 2019 it commenced the production of **food supplements**, again in orodispersible film form.

The productions with a **higher technological and innovative content** manufactured at the plant include orodispersible film (ODF). A patented technology has allowed IBSA to become one of the few companies in Europe to manufacture both pharmaceutical and nutraceutical products.

A second field of production with a high technological and innovation content are the medicated transdermal patches based on drug-in-adhesive technology that allows controlled release of the medicinal product.

The plant covers a total surface area of 20,500 m², including research and development laboratories, a dedicated quality control department and offices. The production areas and warehouse occupy an area of 5,450 m² and utilities 3,404 m². 96 collaborators work there.

Production focuses on the following technologies and pharmaceutical forms:

- Medicated patches for topical and transdermal administration
- Patches with natural active ingredients for cosmetic applications and medical devices
- Orodispersible film (ODF)

Annual productive capacity for the various pharmaceutical forms is:

- Topical patches:
 - transdermal patches 25 million units
 - orodispersible film 4 million units
- Nutraceuticals in ODF 55 million units

The products manufactured at the Cassina plant serve both the IBSA Group and directly supply a number of markets, including, in addition to Italy, France, England, Hungary, Slovakia, Czech Republic, Spain, the Baltic Republics, Scandinavian countries, the EMEA area and South America.

AUTHORISATIONS

- The Quality System is certified in accordance with ISO 9001: 2015 and ISO 13485 2016 (IMQ)
- AIFA authorisation and GMP compliance certificate (Directive 2001/83/EC and Legislative Decree 219/2006) for:
 - production, primary and secondary packaging, control of non-sterile medicinal products ("impregnated matrices", transdermal patches, orodispersible film)
 - manufacturing of non-sterile investigational medicinal products ("impregnated matrices", transdermal patches, orodispersible film)
- Authorisation for psychoactive and psychotropic substances (Italian Presidential Decree 309 of 09/10/1990)



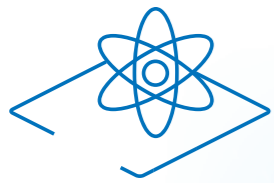
ODF



Patches

Year	2010
Surface	10,500 mq
Collaborators	96
Therapeutic doses	75 mio/year













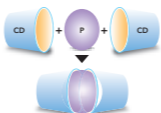









Technologies

Therapeutic solutions for more evolved care

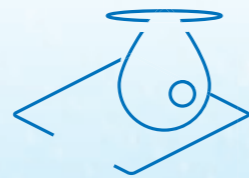
At IBSA, innovating is our daily challenge, the focal point of all our operations, and whose origin lies in a brilliant insight: to transform existing therapeutic solutions with known properties into simpler, more evolved instruments of care.

We are committed to breathing new life into sectors that are often overlooked, by using state-of-the-art technologies to improve the bioavailability of the active substances of commonly-used medicinal products, and developing delivery systems that are more compatible with the real needs of individuals, in order to improve their Quality of life.

To this end, over the years, our Researchers have developed innovative technologies, novel formulations and delivery systems better suited to care.

PHARMACEUTICAL FORMS	PRODUCT CATEGORY			
	Drug	Medical Device	Nutraceutical	Cosmetic
Gonadotropins purification process				
Orodispersible film (ODF)				
Softgel capsules				
Pre-filled syringes				
Progesterone & β ciclodestrine				
Single dose strips				
Patches: medicated, with natural ingredients and for basic medication				
BoV (Bag-on-Valve)				
Nahyco® Hybrid Technology				
Device for intravesical infusion (GAG)				

Purification process



Given the demanding challenge that the medically-assisted procreation (MAP) area represents for the pharmaceutical sector, IBSA has **patented exclusive extraction and purification processes** and installed equipment dedicated to the production of fertility hormones, gonadotropins, using the urine of pregnant and post-menopausal donors.

Gonadotropins are glycoprotein hormones composed of two non-covalently associated protein subunits - the alpha subunit and the beta subunit. The alpha subunit contains 92 amino acids (AA) and is identical in FSH (follicle-stimulating hormone), LH (luteinising hormone) and HCG (human chorionic gonadotropin). The beta subunits, on the other hand, differ and confer receptor specificity and different biological properties. The extent and characteristics of the post-translational changes of these molecules give different charges, biological activities and half-lives to each type of glycoprotein.

The fertility hormone range is produced in compliance with the highest purity, efficacy and safety standards, whilst keeping the structure of the glycoproteins intact. Combining advanced technologies with a full awareness of the relationship between the structure and function of gonadotropins has made the processes patented by IBSA a quality benchmark.

This purification process consists of two steps:

a- Collection of urine from post-menopausal or pregnant women and initial purification

Every day, under IBSA's supervision, the urine of pregnant or post-menopausal donors is collected in rural Chinese villages. Each donation of pregnant or post-menopausal urine is selected on the basis of conformity with specific stringent chemical and physical parameters and is obtained from healthy women who are recruited and monitored by means of preliminary and regular medical examinations. The urine pools obtained are promptly transported to IBSA's Chinese plants, where they undergo further, more thorough quality controls. The approved urine then undergoes a number of purification steps (ultrafiltration, precipitation, filtration, chromatography, drying, etc.) in separate systems. Certain production lines are used solely for the purification of urine obtained from pregnant women and others are used to process that from post-menopausal women, in order to obtain semi-purified solid intermediates with batch sizes of a few kilograms to be sent, under controlled-temperature conditions, to the IBSA plant in Lamone, in Switzerland. Only those intermediates that meet the standards with regard to purity, specific activity and viral safety (absence of contamination from viruses such as HIV, HBV and HCV) are sent to the Biological Active Ingredients Department in Cadempino and Lamone.

b- Final purification and vial-filling

The ultrapurification of the gonadotropins, the most important step in the entire production process, takes place in the Biological Active Ingredients department of IBSA's Swiss plants in Cadempino and Lamone. Before being forwarded for the purification cycle, the dried extracts undergo stringent testing in the Quality



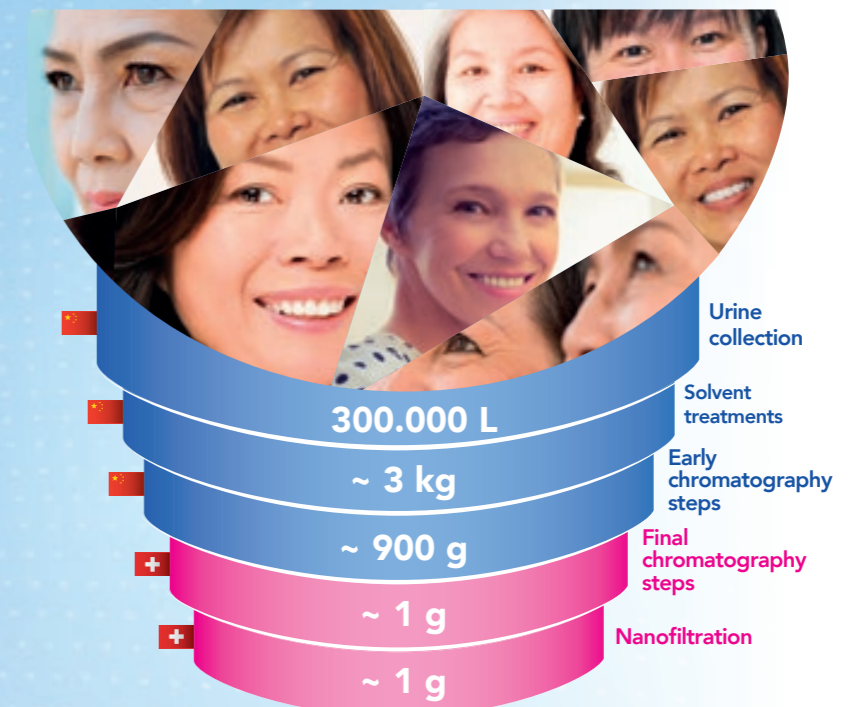
Control department in order to confirm their compliance with quality specifications.

All the purification steps are conducted in cold rooms, i.e. controlled-temperature areas, in order to prevent the degradation of the process intermediates.

The first purification step consists in the weighing of the starting intermediate and its subsequent extraction by dissolution in a special buffer solution. The core of the gonadotropin purification processes is constituted by the liquid chromatography steps using agarose resins that guarantee the achievement of excellent levels of purification whilst preserving the structure.



PROCESS SUMMARY



Special attention is dedicated to the NANOFILTRATION step, which represents the most efficacious barrier for removing all viral contamination from the product to further improve its safety. This technique is able to eliminate even the most resistant (non-enveloped) viruses and prions, protein pathogens that replicate rapidly and are responsible for transmissible spongiform encephalopathies. In addition, the quality of the purified product is monitored during purification by means of in-process controls on all the fundamental parameters. At the end of the process, the purified hormones, in batches of a few grams, are freeze-dried, in a sterile environment, in single-dose vials, to obtain the finished product.

110.000
vials of 75 IU marketed
worldwide



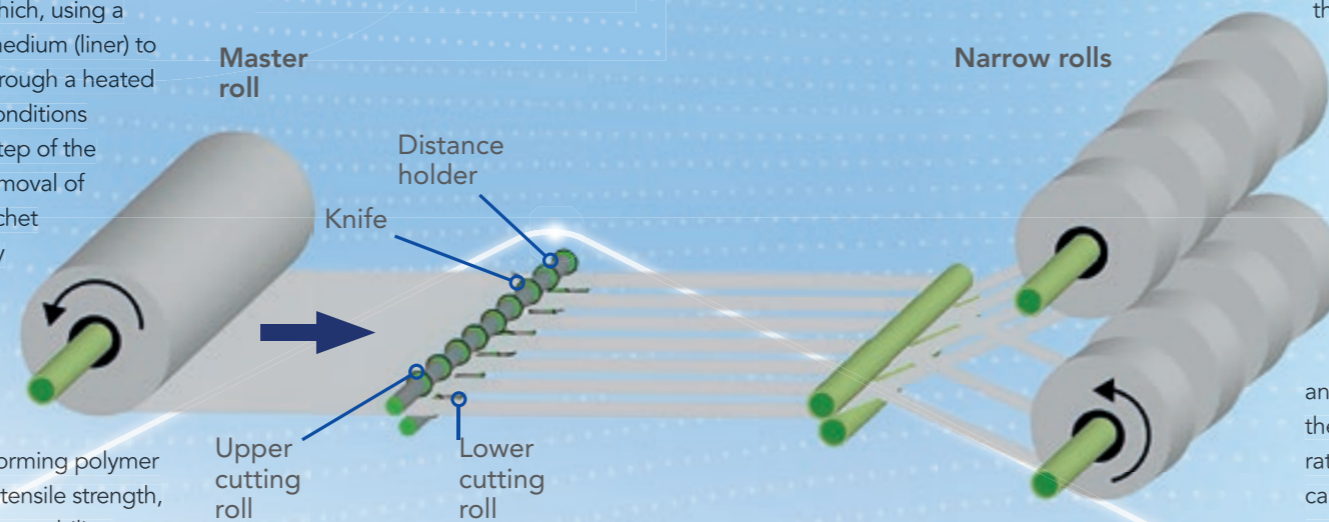
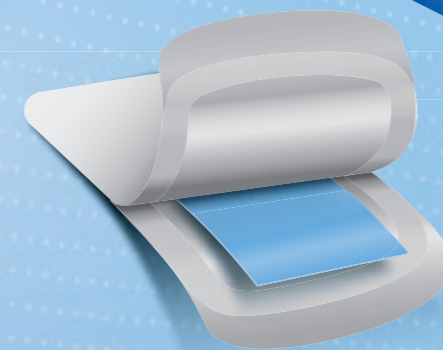
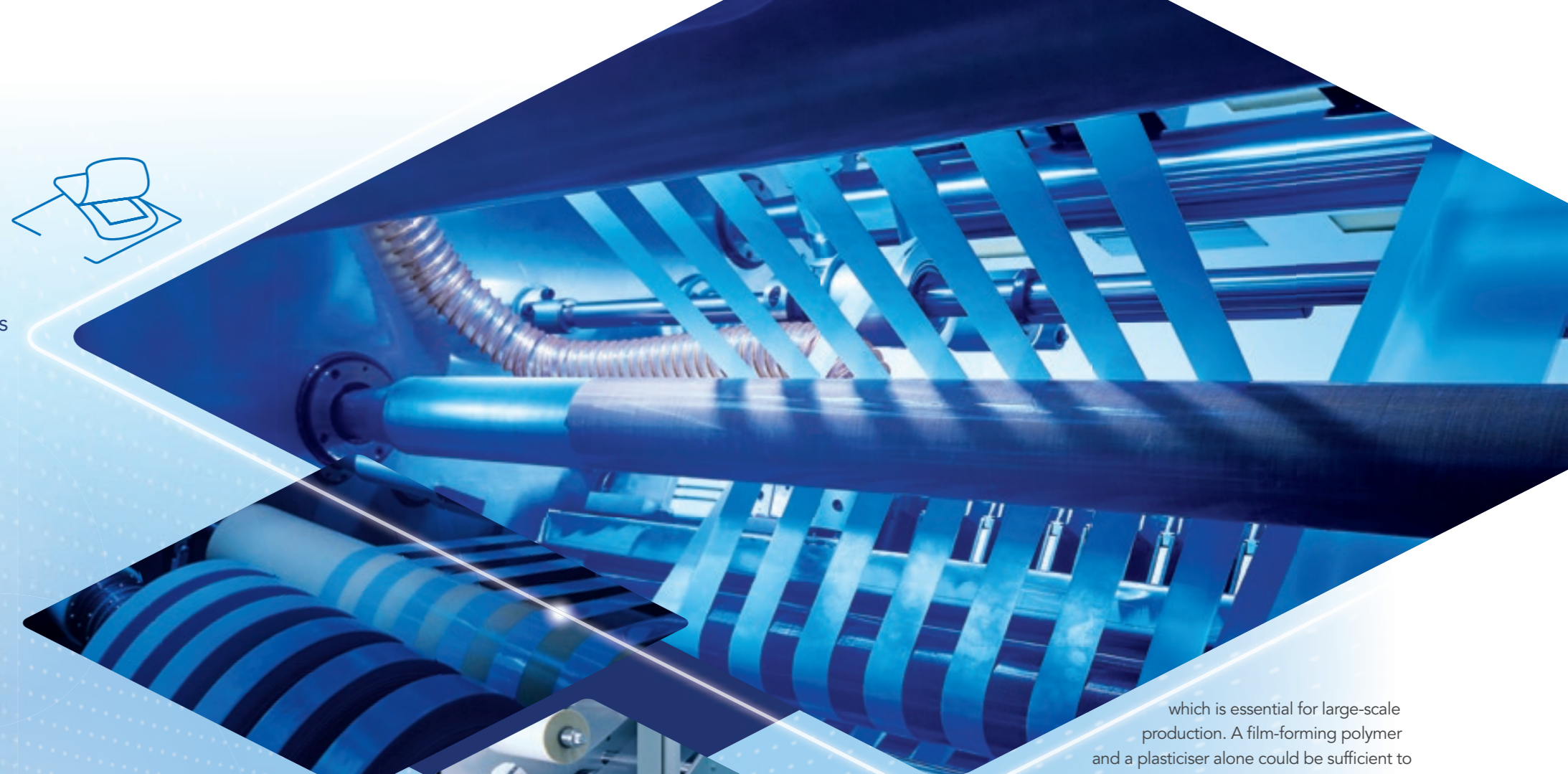
Orodispersible films - ODF

Orodispersible films (ODF), also known as orosoluble films or simply oral films, are a new oral pharmaceutical form, whose characteristics are able to **improve the treatment compliance of certain groups of subjects whose needs are not met by capsules and tablets.**

They take the form of small, thin, flexible sheets, similar to postage stamps that, when placed inside the mouth, dissolve rapidly in contact with saliva. The dissolution time is usually a few dozen seconds and in any case no more than one minute. The weight of a single film is usually a few hundred mg, meaning that very little saliva is required for dissolution. ODFs are normally individually-packaged in heat-sealed sachets, in order to preserve their mechanical properties, avoid contact with atmospheric humidity and guarantee adequate stability. Individual packaging, combined with a limited size and weight make the individual dose unit convenient and discrete, even for use outside the home, in all situations, because it does not need to be taken with water. The use of ODFs is still limited to just a few applications, due to their complex manufacturing process (very limited number of companies are able to master this technology on an industrial scale).

The main production technique for ODFs is based on the **coating process**. In this case, the first step of production is the preparation of a homogeneous coating mass in which all the ingredients are dissolved in a suitable solvent, usually it's water – it's possible to incorporate other poorly-soluble active substances or functional ingredients into this mass, provided they are homogeneously dispersed. In order to achieve this aim, it is necessary to act both on the particle size of these insoluble ingredients, which must be suitably fine and poorly dispersed, and on the dissolver tank stirring system in which the mass is prepared, which can be also fitted with a turbo emulsifier. The coating mass is then used to feed a continuous coating machine inside which, using a calibrated blade, it is distributed evenly over a ribbon of plastic medium (liner) to obtain a layer with an even, pre-set thickness. This then passes through a heated tunnel, where the water is made to evaporate under controlled conditions until the orodispersible film takes on its definitive form. The last step of the process involves cutting the film down to single dose unit size, removal of the supporting liner and individual packaging in a heat-sealed sachet of compound material. The ODFs obtained by coating are usually square or rectangular, with a thickness of a few hundred microns and sides with lengths that can vary from 1 to 4 cm.

A correct coating process makes it possible to guarantee a uniform content in line with the pharmaceutical requirements, ensuring that the concentration of active ingredients is constant over the entire area of the film. Thanks to the water-soluble film-forming polymer that constitutes the main structure of the film, the ODF has good tensile strength, elasticity and flexibility. These properties give the ODF good manageability, which is extremely important for the user, and appropriate processability,



which is essential for large-scale production. A film-forming polymer and a plasticiser alone could be sufficient to obtain an ODF; however, these two ingredients are usually combined with a flavouring, to improve palatability, and a colouring, to improve its appearance. As mentioned previously, the main ingredient of an ODF is the film-forming polymer, which can also be a blend of two or more polymers. There are a number of water-soluble polymers that can serve this purpose, including pullulans, alginates, modified cellulose and maltodextrins. It is important for the polymer to have not just the right solubility, processability, manageability and stability characteristics, but also that it has a neutral or pleasant flavour and does not leave residues in the mouth.

For the production of its orodispersible films, IBSA chose maltodextrins as the main polymer, taking to industrial scale a patented formulation platform that forms the basis of the **IBSA FilmTec** Technology. Maltodextrins have the advantage of being a common, affordable food ingredient with good palatability and rapid dissolution times inside the mouth, where they dissolve completely without leaving an aftertaste.

Orodispersible films always permit immediate release: ODFs release their ingredients very rapidly and can therefore make their absorption easier and quicker than with a tablet or capsule. In certain specific cases, depending on the nature of the active substance, ODFs can also improve the absorption of active substances and functional ingredients.

Orosoluble preparations such as ODFs are the preferred oral form for most people. For certain user categories, such as dysphagic, bed-ridden and elderly subjects, those who have problems taking water and children, the use of ODFs instead of conventional oral forms becomes a necessity rather than a mere preference. As a matter of fact, when compared to tablets, capsules, powders and syrups, orodispersible films allow a precise and accurate dose even for those who have problems swallowing or cannot use water to aid administration.

Soft capsules



Soft capsules were invented in the 1930s to conceal the unpleasant taste and smell of medicines. Since then, **production techniques have greatly improved**. It has been estimated that over 40% of active pharmaceutical ingredients (APIs) have poor biopharmaceutical properties, such as poor water-solubility and/or permeability.

These characteristics are somewhat problematic for the oral bioavailability of compounds that need to be formulated as medicines that are bioavailable when taken by the oral route.

The oral administration of certain medicinal products as solid pharmaceutical forms (e.g. tablets) is a technologically arduous challenge, because certain active ingredients can be oily or poorly soluble in water.

PEARLtec technology is a process for obtaining **softgel** (soft capsules) that makes it possible for a liquid matrix, in a suspension or a gel, to be incorporated into a continuous soft gelatine shell, thereby improving both the oral intake of the medicinal product and patient compliance.

The first step consists in weighing the capsule ingredients, before they are processed using dedicated machines known as turbo emulsifiers. During this part of the process, the optimally balanced excipients are blended together and prepared for the next step.

The heart of the process is the encapsulation step (PEARLtec). The mass that will form the capsule shell is hot-extruded into two ribbons that pass through two roller moulds positioned opposite one another, and that give the capsule its shape. A high-precision syringe pump then injects the previously formulated active substance, inside a mass known as filler, into the capsule being moulded.

This makes it possible to obtain tiny transparent beads consisting of two heat-moulded shells.

During the formation of the capsule, all the essential and critical parameters are monitored by means of in-process controls. This makes it possible to keep the quality of the finished product under control.

Before packaging, the dried capsules are inspected one by one in order to eliminate any flaws.

The quality and stability of the finished product are further guaranteed by special primary and secondary packaging.

In short, this technology makes it possible to take a liquid solution in a solid pharmaceutical form, which is highly advantageous for very low concentration formulations, as it ensures dose uniformity.

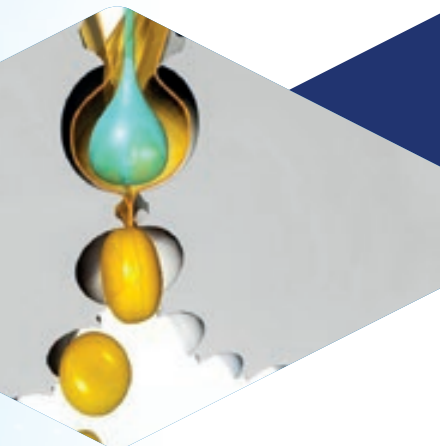
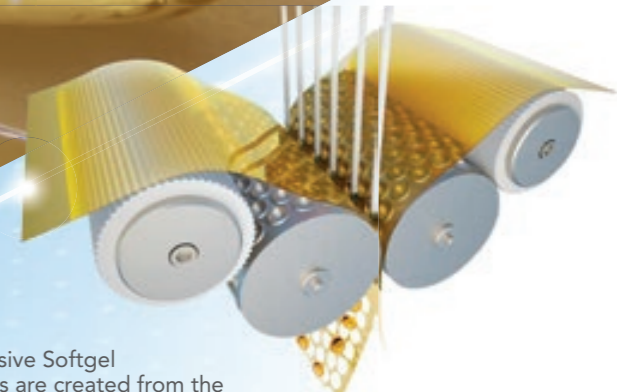


ADVANTAGES

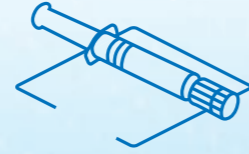
- High dosing precision and better oral bioavailability than other oral solid forms;
- Excellent dissolution profile, regardless of the pH;
- Ease of oral administration;
- Neutral or flavourless taste.

Produced with the exclusive Softgel technology, soft capsules are created from the fusion of two fluid gelatine films in a rotating mould machine.

Just before the sealing of the capsule, the solution containing the active substance is injected using a micro-pump. This process takes place at a temperature of 40°C.



Pre-filled syringes



The manufacture of medicinal products and medical devices often involves the use of ampoules and vials containing ready-to-use solution or powders to be dissolved at the time of the injection. This type of packaging **ensures good product protection, but also makes its administration rather complex.**

The liquid (or powder after dissolution) must be drawn out using a syringe, by piercing the membrane on the vial or snapping the tip off the glass ampoule, operations that require both dexterity and experience. Self-administration is difficult, and the risk of dosing errors and contamination relatively high.

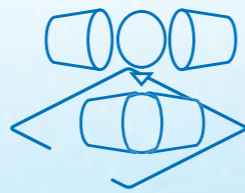
The use of syringe vials, i.e. syringes pre-filled with the right volume of product, greatly simplifies the administration of sterile products for injection and reduces the risk of errors, consequently improving safety. The ease of use favours self-administration and use in emergency situations, in which the injection must be performed as rapidly as possible. It avoids the risk of bubbles forming in the syringe and the risk of contamination, which are always present when products are drawn from ampoules or vials. Pre-filled syringes guarantee a certain dose, with complete product recovery, and ensure sterility. IBSA production lines are able to manufacture sterile pre-filled syringes with different capacities, formats and materials. The presence of highly-automated lines make it possible to achieve high production volumes, whereas the predominant use of glass syringes, combined with a rigorous control of product interactions with the packaging, makes it possible to guarantee the quality and stability of medicinal products and medical devices for injection.

Sterility is obtained by processing under aseptic conditions or by terminal sterilisation.

More specifically, terminal sterilisation in an autoclave is the process of election for high-viscosity solutions. For this type of product, conventional packaging in ampoules and vials is even more disadvantageous and the use of pre-filled syringes is the best technological solution. IBSA has therefore installed lines dedicated to the manufacture and filling into pre-filled syringes of high-viscosity solutions, such as hyaluronic acid solutions for intraarticular and intradermal injection.



Progesterone & β Cyclodextrin



IBSA's research and development has allowed it to place on the market **the only progesterone formulation in an aqueous solution**, which can be administered subcutaneously.

This new formulation is used for luteal phase support in Artificial Reproductive Techniques programmes.

The brainwave that resulted in IBSA developing progesterone for subcutaneous administration was to use a new highly-purified hydroxypropyl- β -cyclodextrin (HPBCD), to increase the solubility of progesterone by exploiting the chemical properties of these molecules. The research conducted by IBSA had shown that the HPBCD products available on the market were not of a purity such as to allow the stability of the HPBCD-progesterone solution. IBSA, in conjunction with Roquette, developed and synthesised a new high-purity HPBCD.

From a chemical standpoint, hydroxypropyl- β -cyclodextrins are cyclic oligosaccharides with an outer hydrophilic part and a lipophilic core that are able to form a complex with hydrophobic drugs, thereby increasing their water solubility.

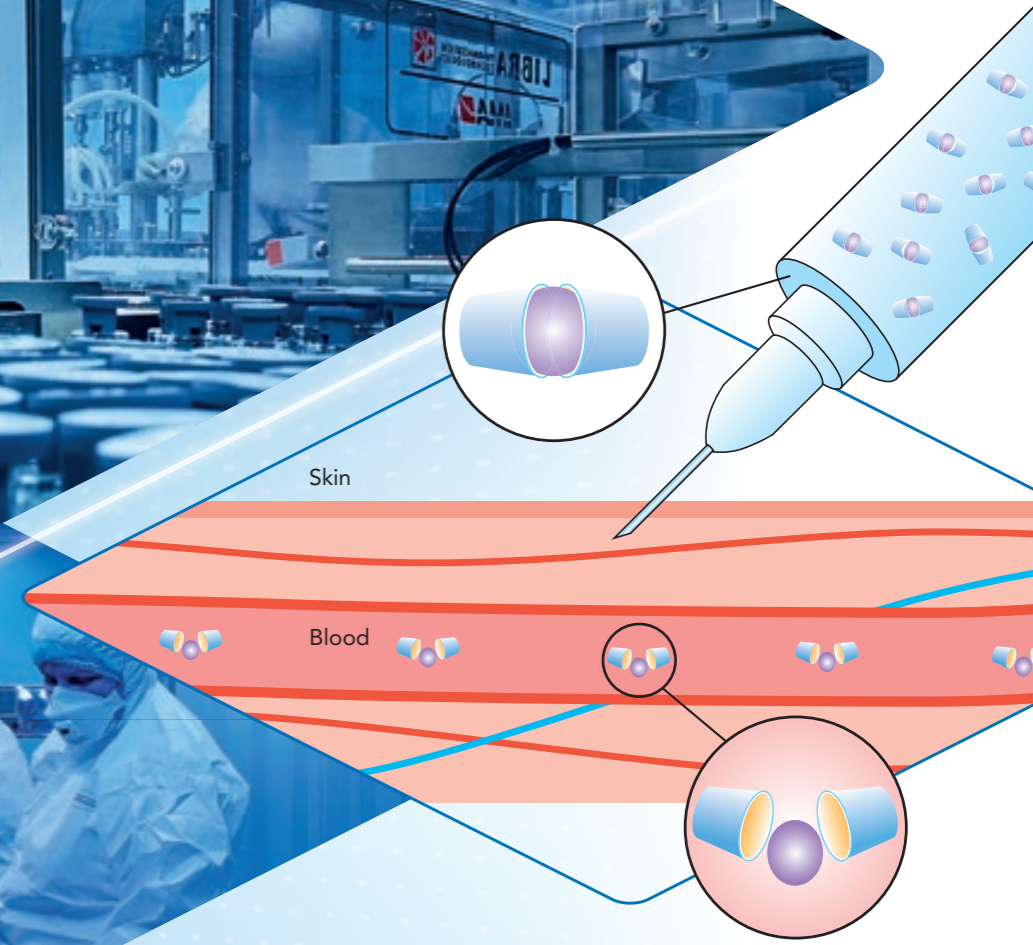
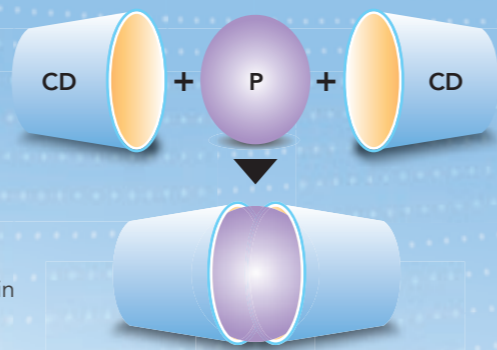
The resulting complex is readily absorbable and can be administered via the subcutaneous route, making administration more patient-friendly than vaginal and intramuscular preparations.

As progesterone is not water-soluble, most of the preparations available on the market are oil-based (ethyl oleate, seed or peanut oil).

As it is a hydrophobic molecule, until now it could not be administered subcutaneously or intravenously.

The new water-soluble progesterone formulation patented by IBSA, on the other hand, can be administered via the subcutaneous route, thus facilitating patient compliance.

Once it has been injected and absorbed, the progesterone molecule immediately breaks away from the complex with hydroxypropyl- β -cyclodextrin and is released into the bloodstream, as though the hormone had been produced physiologically by the corpus luteum.



Single dose strips

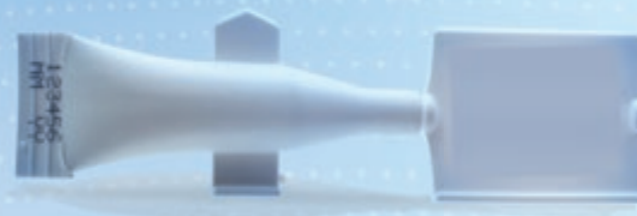
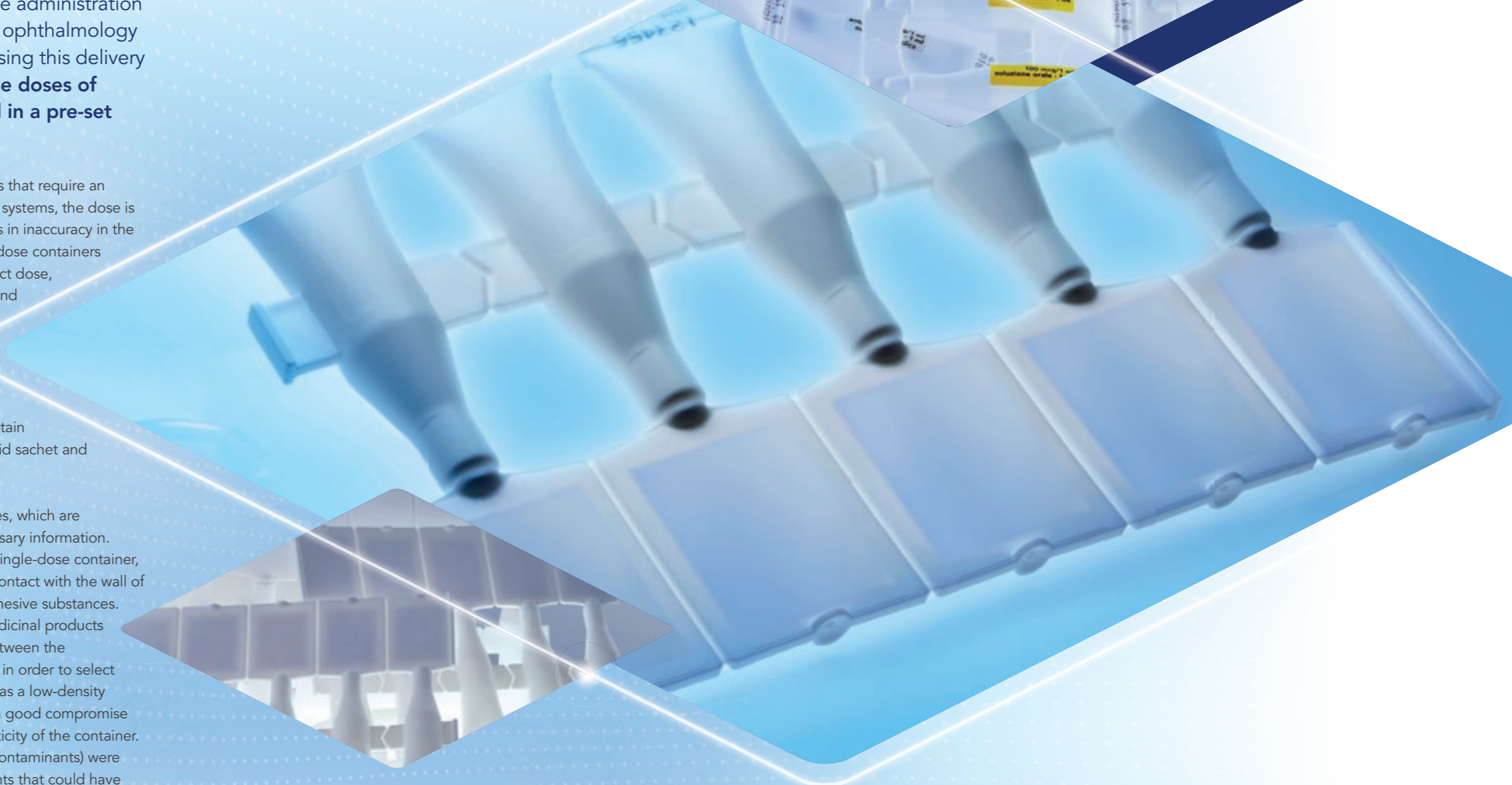
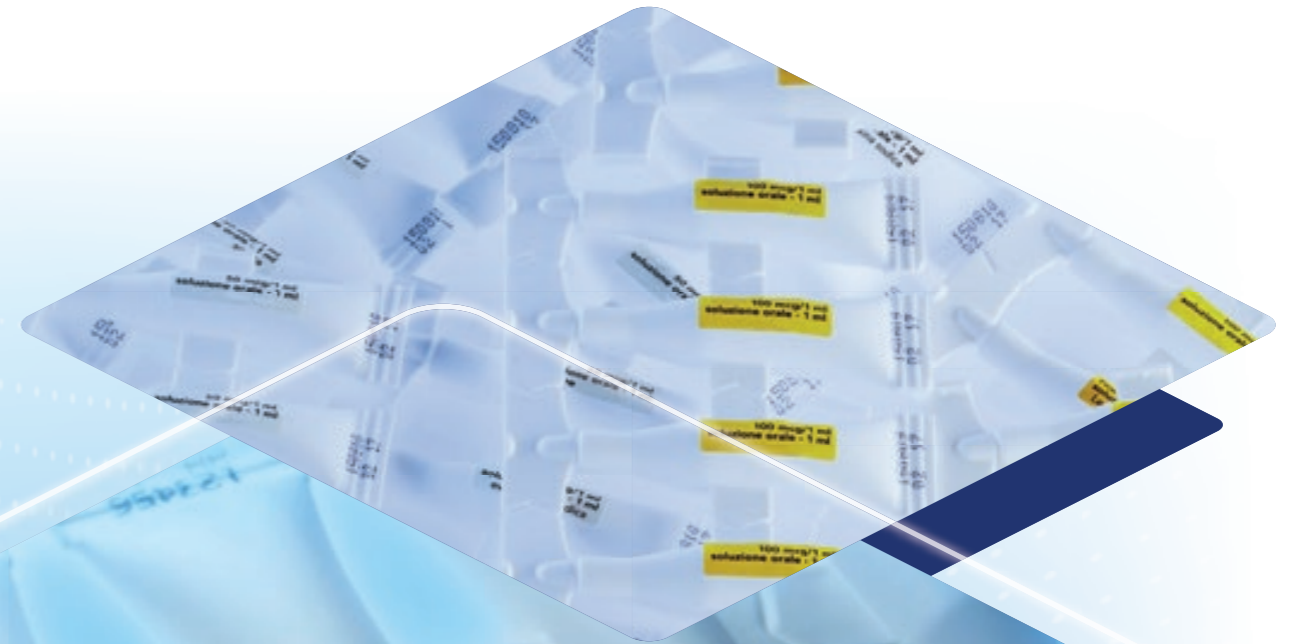


Polyolefin plastic single-dose units are a common primary packaging solution that is often used for the administration of single-use liquid products (typical of the ophthalmology sector). The IBSA innovation consisted in using this delivery system to **guarantee the release of precise doses of medicinal products for oral use dissolved in a pre-set volume.**

Thyroid hormones (T4 and T3) are highly active molecules that require an exact therapeutic dose; however, with multidose delivery systems, the dose is managed by means of the number of drops, which results in inaccuracy in the administration of the prescribed dose. The use of single-dose containers also makes it possible to provide the patient with the exact dose, ready to use at the dosage prescribed by the specialist, and avoids the need for an excessive use of preservatives, which are indispensable for multidose formulations. During manufacture, once it has been prepared in a dissolver tank, the pharmaceutical solution is dispensed using special filling and sealing machines that, starting with an open, empty strip, make it possible to obtain the finished product ready to be packaged in the aforesaid sachet and then in the outer box.

Single-dose strips make it possible to obtain pre-set doses, which are indicated on a colour-coded label providing all the necessary information. This label can be applied to the removable part of each single-dose container, making it possible to prevent it from coming into direct contact with the wall of the container, which could cause contamination by its adhesive substances. The decision to use this type of packaging for certain medicinal products was based on preliminary studies on the compatibility between the ingredients of the solution and different plastic materials, in order to select the best container closure system. The resulting choice was a low-density polyethylene (LDPE) polymer, which is considered to be a good compromise also in terms of softness, which is crucial for the final elasticity of the container. Appropriate studies of the leachables and extractables (contaminants) were also conducted to determine the presence of contaminants that could have been released during contact with the packaging materials.

In literature, injection-moulded LDPE devices are described as semi-permeable containers due to their porous nature that allows volatile chemical products, i.e. substances with a moderate to high steam pressure, to permeate the container. The airtight secondary packaging was added to prevent this from happening.



Transdermal and topical patches



IBSA possesses the technological know-how to develop and produce in its plants single- and multilayer medicated patches designed to act either locally or systemically, depending on the site of action of the active substance.

Both types, which are produced using **Hydrogel and Drug-in-adhesive technologies**, are patent-protected, and this know-how sets IBSA apart in the European pharmaceutical sector, as one of the few companies in the world to be able to offer both.

The structure of these patches is usually composed of a polyacrylate, silicone or other adhesive matrix containing the active substance, a support layer and a protective layer to be removed before application; it can also be more complex, for example, include multiple layers of adhesive containing different concentrations of the active substance.

Patches for topical use can be either formulated to have a local action over a limited area (e.g. diclofenac and piroxicam) or transdermal, with a systemic action (e.g. nitro-glycerine and fentanyl).

Patches for topical use are able to release a medicinal product in a controlled manner, over periods of time that vary from a few hours to a week, offering a great many advantages over oral administration, such as:

- maintenance of optimum concentrations of the medicinal product;
- reduction in the frequency of administration;
- better tolerability.

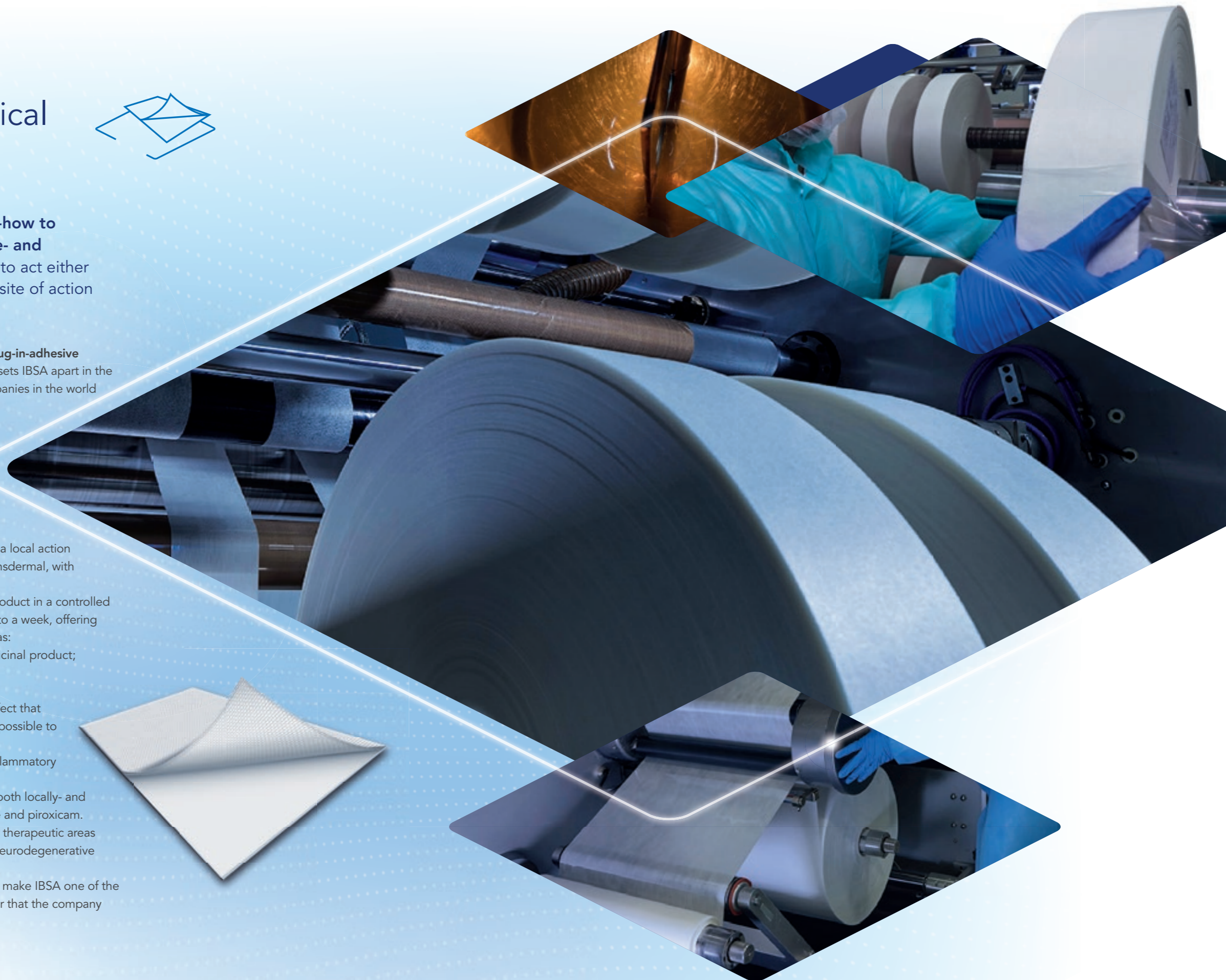
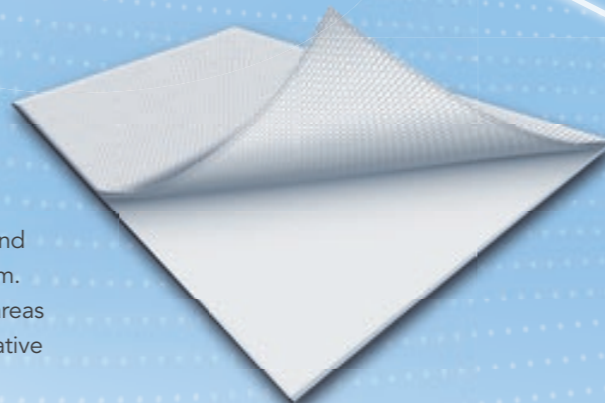
Lastly, use of patches eliminates the hepatic first-pass effect that occurs with oral administration and, in general, makes it possible to optimise bioavailability and reduce side effects.

The field of application ranges from patches with anti-inflammatory activity to those with dermatological activity.

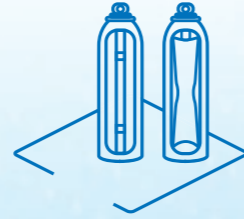
IBSA currently places on the market patches containing both locally- and systemically-released diclofenac, fentanyl, nitro-glycerine and piroxicam.

We are also developing products for application in other therapeutic areas including the cardiovascular and dermatological fields, neurodegenerative diseases and pain therapy.

Its vast technological know-how and productive capacity make IBSA one of the world's leading manufacturers of topical patches, a sector that the company has innovated by filing a number of patents.



Bag on Valve - BOV



A great many pharmaceutical, medical and personal hygiene products take the form of semisolids (creams and gels) or liquids in sprays (aerosols). The packaging traditionally used for these forms are flexible aluminium or plastic tubes for creams and cans with propellants or a pump dispenser for liquid sprays.

In order to overcome some of the limits of conventional packaging and to obtain a more versatile solution suited to diverse products, IBSA has introduced into its plants the **Bag-on-valve (BoV)** packaging technology. In this type of packaging, the product, be it solid or liquid, is placed inside a protective bag, consisting in a laminated, heat-sealed multiply (aluminium and plastic) bag. This bag, the top of which is fitted with a dispenser valve, is contained inside an aluminium can. The system is completed by a dispenser button that, when pressed, activates the valve to release the product inside the bag.

In conventional packs, the product is dispensed due to the force applied by the user, who squeezes the tube of cream or presses the dispenser pump on the spray can. Alternatively, in the case of pressurised aerosol cans, the product is dispensed thanks to its being mixed with a compressed gas: when the user presses the button, the gas is released, taking with it the product and creating the spray.

In BoV packaging, the force that is exploited to dispense the product is again a compressed gas; however, in this case, the gas is not mixed with the product, rather it is pressurised into the space between the bag containing the product and the can containing the bag. This affords a number of advantages over conventional packaging, tubes or propellant sprays:

- the product does not come into contact with the pressurised gas, which is not an ingredient of the formulation
- as it is not necessary to modify the formulation, BoV technology is far more versatile and can be used not only to package liquids (sprays), but also creams and gels.
- product dispensing is practical, uniform, complete (>99%) and possible in any position (360°).
- there is a reduction in the environmental impact, because the compressed gas is air or nitrogen and it is not released into the atmosphere during dispensing, which also prevents the cooling of the product that is associated with propellant sprays.
- the type of gas used, which is harmless and non-flammable, also makes BoV packaging safer.
- the product contained inside the BoV bag never comes into contact with the exterior, even after dispensing. Therefore, compared to a conventional tube, it affords better protection, for example against atmospheric oxidation, longer stability and lesser need for preservatives. In the case of sterile preparations, sterility is preserved even after the first dispensing.

On account of its versatility and advantages, IBSA uses BoV packaging technology to manufacture medicinal products, medical devices and cosmetics in both cream or gel and liquid form.



Nahyco® Hybrid Technology

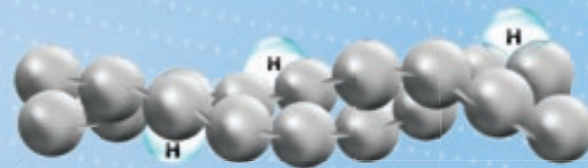


Hyaluronic acid (HA) is a substance that is produced naturally by the human body, in which it is found in the highest concentrations in the dermis and synovial fluid. It serves important functions, such as lubricating and protecting the joint cartilage and hydrating the skin and mucous membranes. The presence of hyaluronic acid decreases physiologically with age or in the presence of certain medical conditions, such as joint diseases. Consequently, in certain situations it **becomes very useful to restore an adequate concentration of HA in the tissues, by means of hyaluronic acid injections.**

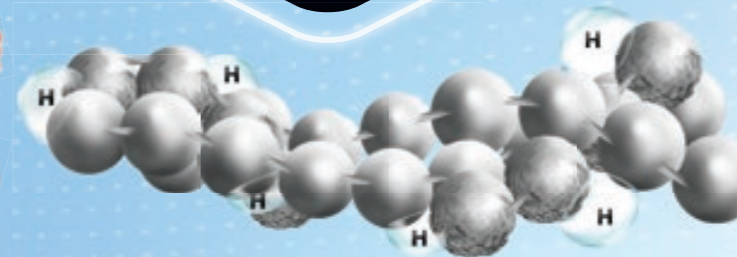
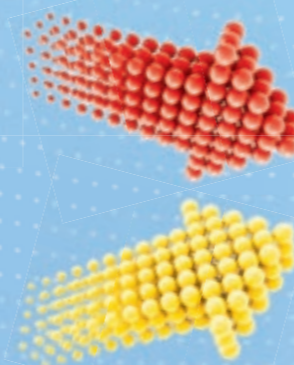
When the injection is made into a large or small joint, the treatment is known as viscosupplementation. This is because the hyaluronic acid present in the synovial fluid gives it the characteristics of viscosity and elasticity required to serve its main functions: lubrication, at rest, and protection (shock absorption), during movement. When the concentration of HA in the synovial fluid drops, due either to age or disease, the fluid loses some of its viscosity and elasticity. Hyaluronic acid supplementation by injection makes it possible to replenish the concentration of the molecule, thereby restoring the synovial fluid's correct function. The effectiveness of the viscosupplementation treatment depends on the extent to which the characteristics of the solution of hyaluronic acid administered mimic the natural characteristics of synovial fluid. With this in mind, IBSA developed and patented NAHYCO® HYBRID TECHNOLOGY, which makes it possible to deliver high doses of hyaluronic acid, thereby improving the viscous and elastic properties of the formulation and improving its resistance to degradation. This technology uses polymer chains of various lengths (i.e. different molecular weights): **by means of a heat treatment, high-molecular-weight hyaluronic acid (H-HA) and low-molecular-weight hyaluronic acid (L-HA) form strong hydrogen bonds to form hybrid cooperative complexes without using chemical cross-linking agents.** This makes it possible to achieve high concentrations of HA without prejudice to the ease and safety of injection and effectively mimicking the physical and mechanical properties of healthy synovial fluid, thereby optimising the concept of viscosupplementation.

The same NAHYCO technology can also be used with success in other indications. It can be used, for example, to replenish the physiological concentration of HA in the skin, improving its water content and consequently the appearance of the ageing dermis. Once again, the possibility of obtaining

H-HA
High Molecular Weight HA



L-HA
Low Molecular Weight HA



THERMAL PROCESS WITHOUT CHEMICAL MODIFICATION⁽¹⁾
A specific and patented treatment of the solution

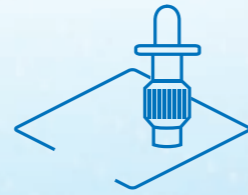
high concentrations and optimised characteristics allows straight-forward delivery of high doses of HA that distribute within the dermis to achieve an optimum result.

At the same time, the technology guarantees absolute safety, due to the use of high-purity hyaluronic acid, obtained by fermentation rather than extraction from animals, and that is identical to that present in the human body, without requiring any chemical modification.

It should also be emphasised that although the NAHYCO technology applies primarily to hyaluronic acid, it can also be extended to mixtures of high-molecular-weight hyaluronic acid and other polymers of the same family (glycosaminoglycans, or GAGs, with include chondroitin). The hybrid cooperative complex can therefore be formed, for example, by combining high-molecular-weight HA with biotechnological sodium chondroitin, where the sodium chondroitin, which IBSA obtains by fermentation using a patented process, serves the same function as low-molecular-weight hyaluronic acid.

Bibliography: 1. WO Patent: WO/2012/032151

Device for intravesical Glycosaminoglycan (GAG) infusion



The urothelium is a type of epithelial tissue that lines the bladder and the urinary tract. The urothelium is covered by a layer of polyanionic molecules constituted primarily by glycosaminoglycans (GAG), a class of sugars that form a protective, neutralising barrier that is impermeable to both toxic substances and microorganisms. Of the various GAGs making up this barrier, **hyaluronic acid and chondroitin sulphate play a key role in its function.**

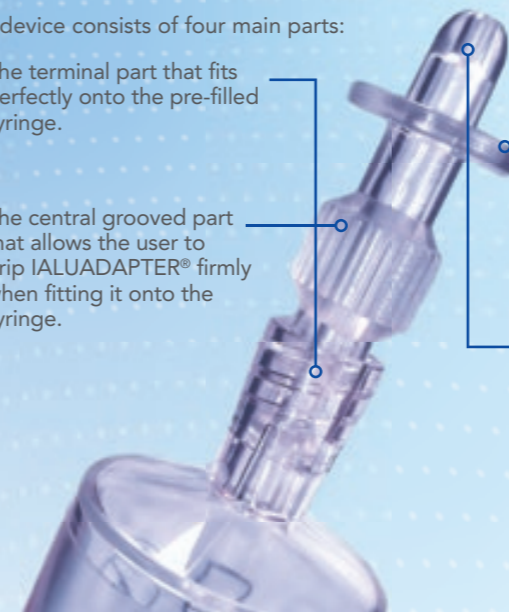
Qualitative and quantitative variations in these two GAGs at different levels eliminate the barrier effect, generating a series of conditions that can favour the onset of cystitis of various types (e.g. interstitial cystitis, recurrent cystitis caused by infection, etc.). Hyaluronic acid (HA) and chondroitin sulphate (CS) are often used for these therapeutic purposes in the form of a very diluted solution of the individual GAGs, delivered using a catheter. The relatively low sodium hyaluronate content is made possible by its physical and chemical characteristics and its aqueous solutions present an excessive increase in viscosity with concentration. Therefore, an indiscriminate increase in the concentration of the active substance (despite its excellent water-solubility) is not feasible for the therapeutic purposes considered here, because the consequent substantial increase in viscosity would make the administration of the solution by catheter difficult and painful. It is also known that combining hyaluronic acid with chondroitin sulphate produces an excessive increase in viscosity due to the two molecules' propensity to clump together. IBSA research found a surprising solution to this problem by discovering that hyaluronic acid can be combined with chondroitin sulphate using bivalent metal ions that act by reducing the viscosity of the solution.

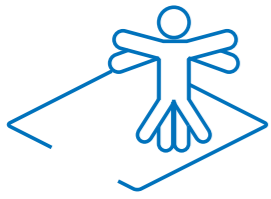
The product developed by IBSA consists in a 50-mL Crystal Clear pre-filled syringes (1.6% HA, 2% CS, 0.87% CaCl₂) and a novel patented medical device (IALUADAPTER®) that makes it possible to inject a glycosaminoglycan solution into the bladder using a minimally-invasive procedure without requiring catheterisation. IALUADAPTER® can be an alternative to the use of standard male and female catheters and its main advantage is that it eliminates the pain associated with the catheterisation procedure. As, using IALUADAPTER®, the solution passes straight into the bladder through the urethra, it simultaneously treats both the urethral and the vesical mucosae. IALUADAPTER® is designed to fit snugly against the opening of the urethra, to allow the fluid to flow into the bladder without leakage of the solution.



The device consists of four main parts:

1. The terminal part that fits perfectly onto the pre-filled syringe.
2. The central grooved part that allows the user to grip IALUADAPTER® firmly when fitting it onto the syringe.
3. The concave insulating collar made of elastic material that adjusts to fit the surface surrounding the orifice and facilitates delivery without solution leakage.
4. The short blunt tip, the only part of the device that penetrates into the opening of the urethra.





Therapeutic areas

Our commitment to research in 10 Therapeutic Areas

Our mission is to **find efficacious therapeutic solutions** in those sectors that are often overlooked, **by using state-of-the-art technologies to develop treatment systems that better suit people's real needs.**

We are firmly convinced that providing care means taking care, in the broadest sense of the term. We achieve this by listening to patients and doctors, because this two-way communication allows us to understand real care needs. This is what we do with our research in the **10 Therapeutic Areas.**



Osteoarticular



Respiratory



Reproductive Medicine



Dermatology



Endocrinology



Consumer Health



Aesthetic Medicine



Pain and inflammation



Urogynaecology



Cardiometabolic



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