HUVEPHARMA®

ITALIA S.R.L.

Human & Veterinary
Pharmaceuticals

HUVEPHARMA®
ITALIA S.R.L.

www.huvepharma.com

Corporate Vision for Growth

DEAR PARTNER,

As the President of Huvepharma®, I would like to communicate to you our vision for growth and the benefits we can offer to you as a partner.

Huvepharma® is a global organization of structures, which has expanded throughout the years naturally by intensive internal evolvement and numerous strategic acquisitions. Huvepharma® has manufacturing facilities, and sales and marketing organizations around the globe, which establish direct relationships with every customer. The highly efficient integrated structure and the talented human capital allow our company to offer competitive and beneficial business conditions. Huvepharma® group of companies offers premium advantages to its customers and partners, as well as understanding of their needs, which has become an essential component of its continuous growth. As a part of this philosophy, Huvepharma® keeps top quality at all levels, employing highly qualified and experienced specialists in its R&D, production, regulatory affairs, sales and marketing structures.

Huvepharma® group of companies operates manufacturing units in Europe and overseas. The production units in Bulgaria, USA and Italy account primarily for the global production supply, whilst the factories in Turkey and India carry out production activities specifically for the local market. There is a long history and tradition in operation, know-how and expertise, behind this manufacturing force, and this global network is an essential key to our effectiveness and results. Our state-of-the-art production and quality control equipment ensure top quality production and prove our reputation of a highly trusted producer, very flexible in meeting customers' and partners' needs.

The significant investments that have been accomplished over the past years have enabled our company to be responsive to market changes, to develop multi-purpose production, to be more efficient, more competitive and to offer an enlarged product portfolio with registrations in more than 90 countries that we will continue to expand in the future.

Our expertise and management team has developed Huvepharma® into a high-growth international player by integrating acquired companies and fostering new products registrations in key markets worldwide.

We welcome new proposals for partnerships as well as development of innovative products and technologies, understanding the value of collaboration and mutual beneficial relationships.

With respect,
Kiril Domuschiev
President, Huvepharma®

HUVEPHARMA® ITALIA S.R.L.

Huvepharma® Italia's Vision And Mission

The Vision
We grow fast, being leader in Quality, Safety and Environmental excellence, worldwide recognized as qualified partner in supplying human and animal health bulk products and development services, operating in a highly motivated and committed environment.

The Mission
Our daily aim is to establish and to consolidate an effective partnership with our Customers, because we strongly believe that this is the only way to ensure them the best Development Service quality and the best Product quality.

Nicola de Risi
CEO, Huvepharma® Italia Srl

Introducing Huvepharma® Italia

Huvepharma® Italia is a fast-growing global pharmaceutical company duly organized for developing, manufacturing and marketing advanced intermediates and active pharmaceutical ingredients by chemical synthesis for both human and animal health. The focus is specifically on offering services for developing and industrializing new molecules for start-up companies, always operating in a certified GMP environment
Huvepharma® Italia is also particularly active with proven expertise in the fight against malaria disease.

Huvepharma® Italia is a privately-owned company, headquartered in Garessio (CN) – Italy, employing about 150 people.

Huvepharma® Italia operation is located in Garessio (CN), northwestern part of Italy, and consist of a complete independent and autonomous development and manufacturing unit acquired from Sanofi since May 1st 2016.

The product development and manufacturing facilities, operated in accordance with the most stringent quality, environmental, safety and industrial hygiene regulatory requirements, provide a very flexible capacity for developing, industrializing and producing APIs and intermediates for human and animal health.

Particular emphasis is devoted to the process development activity thanks to full equipped laboratories and very flexible pilot unit that allow to develop and industrialize quite complex chemical processes.

Our expertise lies in the creation of a close and trustable partnership with our Customer and in the emphasis we place on best addressing customers' each and every requirement for adding performance to their business. Huvepharma® Italia employs highly skilled individuals with extensive experience in the human health industry, with knowledge of their local markets and customers, who can further count on a very qualified network of external advisors.

Huvepharma® Italia commercial and business development offices are also located in Garessio (CN), Italy, and consist of a very qualified team available to support the Customers globally.

Huvepharma® Italia works also extensively for the cause to fight malaria disease. It has proven proficiency in the field and partnership in key projects.

HUVEPHARMA® ITALIA S.R.L.

World Presence

Huvepharma® Italia, as part of Huvepharma Group, takes advantage of the worldwide sales network and product distribution of the mother company.

Manufacturing facility
Affiliate / representative office

Huvepharma® head office: Sofia, Bulgaria

Global sales and marketing functions: Antwerp, Belgium

Manufacturing facilities:

- Botevgrad, Bulgaria
- Peshtera, Bulgaria
- Razgrad, Bulgaria
- Saint-Etienne, France
- Segré, France
- Garessio, Italy
- Van Buren, Arkansas, USA
- Longmont, Colorado, USA
- St. Louis, Missouri, USA
- Lincoln, Nebraska, USA
- Laurinburg, North Carolina, USA

Affiliates / representative offices:

- Porto Alegre, Brazil
- Quebec, Canada
- Beijing, China
- Segré, France
- Pune, India
- Kyoto, Japan
- Guadalajara, Mexico
- Warsaw, Poland
- Moscow, Russia
- Gauteng, South Africa
- Taipei, Taiwan
- Bangkok, Thailand
- Istanbul, Turkey
- Atlanta, Georgia, USA

Huvepharma® is represented in other regions through a large network of local distributors.
Visit our website, www.huvepharma.com to find your nearest Huvepharma® representative.

HUVEPHARMA® ITALIA S.R.L.

Company Origin

Huvepharma® Italia is built on the strong foundations and long-standing reputation of the business that make up our Huvepharma® group.

The company has achieved synergies between its management, marketing know-how and development strategy with more than one century expertise and tradition in manufacturing human health products by chemical synthesis. The production facility which was just acquired in 2016 incorporates the competence and the experience of large chemical-pharmaceutical companies like Lepetit, Dow Chemical, Aventis and Sanofi.

Milestones of Our Company History

Huvepharma® Italia key strength lies in chemical synthesis. This expertise has been developed at the Garessio facility for more than one century of manufacturing activity. The excellence in process and technology has been reached thanks to the continuous improvement approach in handling the development and manufacturing activities.

2016 Huvepharma® Italia Srl acquires Garessio production facility, starting to operate on May 1st 2016.

2012 Start-up of the semi-synthetic artemisin (key starting material for anti-malaria medicines) production with innovative photo-oxidation technology.

2005 Garessio production facility acquired by SANOFI.

1999 After successive mergers, Garessio unit is acquired by AVENTIS.

1982-1983 Implementation of several new productions in the Garessio facility including Urokinase, Thrombolytics, Terfenadine and anti-histaminics.

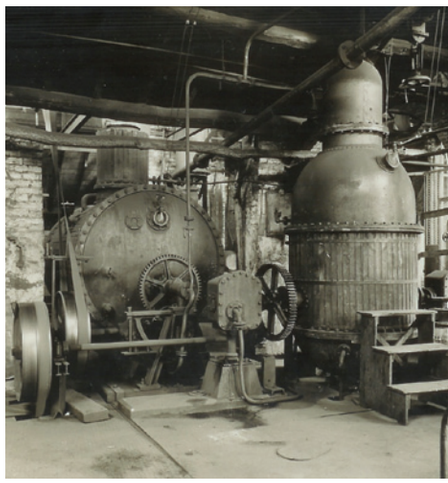
1964 DOW CHEMICAL acquires the majority of the shares of Lepetit S.p.A. and starts up the Garessio production facility, upgrading the technology process with a focus on the safety, environmental, industrial hygiene and quality areas.

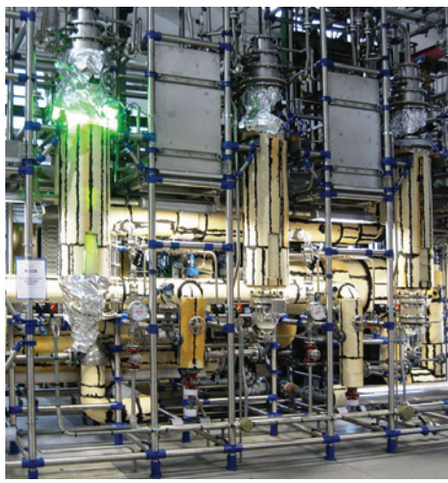
1935-1949 Garessio facility progressively extends its production to the synthesis of vitamin D, vitamin K, vitamin PP, folic acid and chloramphenicol, the fist antibiotic by synthesis produced in Italy.

1930 Garessio facility produces more than 10.000 tons of APIs, chestnut extracts, tanning extracts and inks.

1903 Production of Almateina - the first pharmaceutical product of Garessio and the first to be produced at industrial scale in Italy.

1894 Establishment of Garessio chemical plant by Roberto Giorgio Lepetit founder: area of 8.000 sq.m. and 70 operators.





Manufacturing

Huvepharma® Italia emphasizes quality assurance throughout the entire cycle of production, distribution and use. The Quality Control department executes strict quality control of all incoming materials, critical steps during manufacture (IPCs), intermediates and finished products in accordance with the approved specifications.

The facility offers very flexible chemicalsynthesis capacity for a total reaction volume of 700 m^3, distributed in 100 reactors from a few m^3 up to 25 m^3, in various construction materials (stainless steel, glass lined and hastelloy). The above production capacity is concentrated in 5 manufacturing buildings and 8 production lines that are completed with 4 clean packaging rooms

Complex chemical reactions in large scale are part of Huvepharma® italia core know-how with specific reference to high pressure (up to 50 bars) and big volume (up to 10 m^3) catalytic hydrogenation (homogeneous and etherogeneous) with various catalysts, catalytic carbonylation with co gas, grignard reactions (up to 8 m^3), friedel crafts reactions, gas – liquid reactions (eg by hcl gas), peroxide handling, photooxidation, bromination reactions, etc.
Crystallization controlled by fiber optics and separation of optical isomers are part of the technology know-how of the company too.

More than 50% of the production lines are fully automated using the latest generation equipment and digital technology for interfacing with peripheral devices.

For the needs of the manufacturing process, there are onsite service units like electricity (co generation unit included), air, steam and natural gas distribution facilities, wastewater treatment plant and thermo-oxidizer to treat the overall plant vents outlet streams.

Moreover, we have state-of-the art laboratories for QC testing and analytical development, reference standard preparation and stability studies.

The warehousing facilities meet all the necessary requirements to ensure safe storage.

Thanks to the above expertise, Huvepharma® italia is already recognized as a reliable supplier of development service of apis and advanced intermediates for leaders in the international market (e.g Huvepharma® acts as cmo for api manufacturing on behalf of companies like Sanofi® and Dow®).

R&D Facilities

- We have a team of qualified specialists involved in chemical synthesis of APIs and intermediates
- We're specialized in process development, analytical development and optimization for a quick industrialization and production of validation batches
- We're equipped with modern laboratories to run complex chemical reactions
- We have an acidic resistant pilot plant to test the latest version of the recipes defined at laboratory level and to produce validation batches in GMP environment
- We're used to perform comprehensive safety assessment before running production at lab and pilot scale
- Scale-up activities can be done in any of the other available workshops
- Our group is supported by Regulatory capable of drafting the files for submission in relevant countries (according to EU, US FDA and WHO requirements)
- Typical reactions and technologies applied:
- Oxidations (peroxides)
- Photo-oxidations
- Brominations
- Catalytic hydrogenations
  - various catalysts (Ru, Rh, Pd, Pt)
  - up to 50 bar
  - up to 10 m^3
- Catalytic carbonilation with CO
- Acetylations
- Friedel-Crafts
- Gas liquid reactions (by HCl gas)
- Grignard
- Esterifications
- Optical isomer resolution
- Nano particles production
- Crystallization controlled by optical fibers

Huvepharma® Italia can offer the following Services:

- R&D and Process Development
- Analytical support including Reference Standards preparation via Preparative HPLC
- Products purification by Preparative HPLC
- Production of validation batches
- Dossier preparation and submission to various Agencies
- Toll Manufacturing

Emphasis on Quality

Huvepharma® Italia emphasizes quality assurance throughout the entire cycle of production, distribution and use. The Quality Control department executes strict quality control of all incoming materials, critical steps during manufacture (IPCs), intermediates and finished products in accordance with the approved specifications.

Production steps and processes are carried out in accordance with the GMP, following detailed standard operating procedures and detailed written records are created and kept for each production batch. The management oversees an ongoing training program for the continuous improvement of the qualification of both employees and management.

Our Regulatory team is experienced in dealing with DMF preparation (CTD format), CEPs and dossiers necessary for submissions in Italy, Europe, US, Japan and WHO.

In-depth attention to the quality results in the followings active certifications:

- GMP certificate and manufacturing license issued by the Italian authority (AIFA)
- US-FDA approval for some of the products intended for the US market
- CEPs for some of the APIs
- WHO prequalification for anti-malarial APIs and GMP intermediates
- Japan-PMDA accreditation
- Food Safety Certification 22000

Investing in Environmental Safety Technologies

Huvepharma® Italia manufacturing facility has developed an environmental management system certified in compliance with the requirements of the international standards ISO 14001 since more than 20 years.

A new co-generation plant, a modernized wastewater treatment plant and a thermo-oxidizer, which guarantee environmental protection, reduction of CO emissions and discharge of liquid and air streams in compliance with the more stringent Italian and EU regulations.

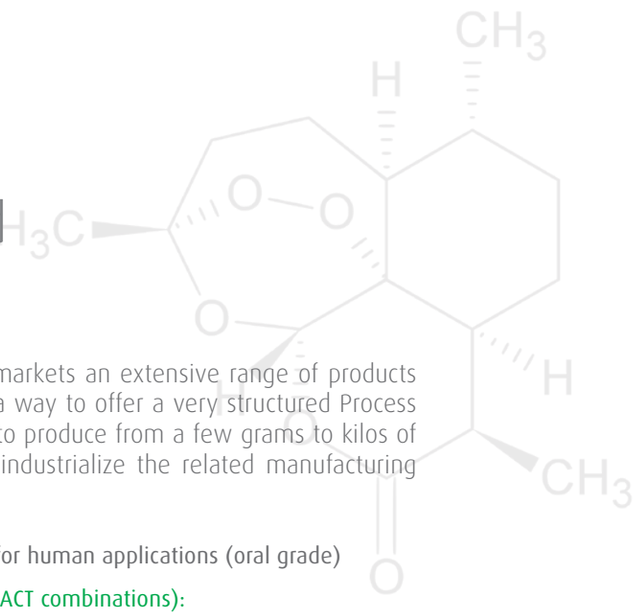
While we are able to handle highly toxic materials in our processes, our first priority is the Safety and the Industrial Hygiene of our experienced personnel.

Diligent attention in every aspect of the process development and manufacturing operations made it possible to get the OHSAS 18001 certification in 2007 and more recently the ISO 45001.

Huvepharma® Italia Operates Globally in a Highly Motivated and Commited Environment

The company is operating on every continent either directly or through its Customers with the same dedication to provide high-quality advanced intermediates and APIs and development services, especially to start-up companies on the USA market.

Our Products and Our Services



HUVEPHARMA® Italia markets an extensive range of products and operates in such a way to offer a very structured Process Development Service to produce from a few grams to kilos of a new molecule and industrialize the related manufacturing process.

THE PRODUCTS

Active Ingredients for human applications (oral grade)

ANTI-MALARIA (for ACT combinations):
- Artesunate (CAS N. 88495-63-0)
- Artemether (CAS N. 71963-77-4)

ANTI-INFLAMMATORY:
- Deflazacort (CAS N. 14484-47-0)

PSYCHIATRY:
- Tiapride HCl (neurological and psychiatric disorders) (CAS N. 51012-33-0)
- Sulpiride (antipsychotic) (CAS N. 15676-16-1)

ANTI-CHOLINERGIC:
- Oxybutynin HCl (CAS N. 1508-65-2)

NOOTROPICS, FOOD ADDICTIVES:
- Potassium N-Acetylaminosuccinate (ASK2) (CAS N. 3397-52-2)

API INTERMEDIATES/ RAW MATERIALS

Semisynthetic Artemisinin (key material for antimalaria APIs) (CAS N. 63968-64-9)
Cis Triol Acetonide (for Nadolol – Heart arithmia) (CAS N. 52187-19-6)
Cortiseven (for Deflazacort – Anti-inflammatory) (CAS N. 21269-13-6)
Ramipril Precursor 1 (For Ramipril – ACE inhibitor) (CAS N. 82717-96-2)
Thiophene ester base (for Articaine – dental anaesthetic) (CAS N. 85006-13-1)
Chloro 2 Phenothiazine (for Chlorpromazine, cyamemazine – anti-psychotic) (CAS N. 92-39-7)

ANTI-FUNGAL
- Anidulafungin (CAS N. 166663-25-8) UNDER DEVELOPMENT

ANTIBIOTIC
- Dalbavancin (CAS N. 171500-79-1) UNDER DEVELOPMENT

THE PROCESS DEVELOPMENT SERVICE

Standardly, the service is carried out through the following key steps and items that are applied to meet the specific requirements of each product/process:

1. SIGNATURE OF THE CONFIDENTIALITY AGREEMENT

2. HEALTH SAFETY ENVIRONMENT (HSE)
- Hazop
- Classification of working spaces (e.g. ATEX, environmental zones)
- Risk assessment (including toxicological assessment)
- Fire Brigade permit impact
- Assessment vs. SEVESO law classification
- Environmental assessment
- REACH registration

3. QUALITY AND REGULATORY
- Quality and regulatory risk assessment
- Validation master plan and validation protocols
- Qualification (DQ,IQ,PQ)
- Definition of analytical methods, adoption or validation, if needed (including particle size analysis)
- Cleaning validation
- Stability studies
- DMF preparation in CTD format if applicable
- Specific regulatory approval from the involved Agency

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