Challenging chemistry requires a skilled partner.
Contents

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2. Our R&D Team & Tools
3. Our Core Technologies: Challenging Chemistry
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Dipharma Group 2019

- Custom synthesis & generic APIs
- All sites inspected by EU authorities and US FDA; AFM & site inspected by PMDA
- > 500 people
- $141 Mio * in product sales
- About 250 patents & applications filed
- 70 years of experience in innovation in handling complex and hazardous chemical processes safely

* 2018, not audited data
Commercial Offices and R&D Laboratories

Kalamazoo, USA
Kalexsyn, Inc.
Acquired in 2018

Baranzate, Milan
Dipharma Francis S.r.l
Renovated in 2009

Kalamazoo, USA
Dipharma Inc.
Opened in 2012

Beijing, PRC
Dipharma China R.O.
Opened in 2015
cGMP production sites

Baranzate, Milan
Dipharma Francis S.r.l.
FDA inspected since 1970

Caronno, Varese
Dipharma Francis S.r.l.
FDA inspected since 1978

Mereto, Udine
Dipharma Francis S.r.l.
FDA inspected since 1980
R&D and cGMP* in the United States
Kalexysyn

Kalamazoo, MI, USA
(R&D, cGMP*)

Kalexysyn, Inc.
Kalamazoo, MI
Founded in 2003

* cGMP 1Q2020, Commercial Certified
## GMP Compliance Status

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<td>2013</td>
<td>AIFA</td>
</tr>
<tr>
<td>2018</td>
<td>AIFA</td>
</tr>
</tbody>
</table>

* AIFA inspection for manufacturing of Pharma Mixtures
* Mutual Recognition Agreement
Mario Biazzi (1897-1974)

Our history
experience innovation

1936  Patented first continuous nitroglycerine unit
      Started the company now named Biazzi S.A.

1954  Instigated & co-founded Safex International (no profit organization)

1956  Delivered world’s largest nitroglycerin plant (2MT/hr.)

1960  Delivered world’s first entirely automated plant for transporting, storing and weighing nitroglycerine

Today, about 70% of the world production of nitroglycerin is made using Biazzi technology.
Our Values

Safety
- Behaviour Based Safety (BBS)
- Reporting of Near Miss and Safety concerns
- Root Cause Analysis (RCA), Failure Mode and Effect Analysis (FMEA)

Quality
- GMP, inspected by US-FDA, AIFA, PMDA, etc. since 1970
- Six sigma (black and green belts)
- Root Cause Analysis (RCA) and Error proof systems

Innovation
- Over 200 patents/applications filed
- Intellectual Property (IP) department
- Suggestion system

Flexibility
- Broad range of technologies and production scale
- Products validated on 2 mfg. sites
- In-sourcing/out-sourcing of intermediates

Productivity
- Lean program, continuous improvement, Value Stream Mapping
- Debottlenecking
- Process Technologists

Ethics
- Loyal customers
- Loyal employees
- Loyal shareholders
Our chemists and senior advisors have key roles in the invention and development of several marketed drugs.

20 medicinal and process chemists at the bench. ~1:1 ratio of Ph.D. to MS/BS.
USA non-GMP Laboratories
Kalexsyn

- Over 20,000 sq ft of lab space. Non-GMP 15000 sf and GMP 5000 sf
- Custom designed chemistry research facility with open lab plan.
- Designed to eliminate exposure (zero-exposure) to scientists.
- 13 linear feet of hood space per chemist.
USA Non-GMP Process Development
Kalexsyn

- Milligram to kilo syntheses using up to 50 L glass reactors.
- Process route optimization.
- Process chemistry re-design.
- Process impurity identification and synthesis.
USA Analytical Equipment

Kalexsyn

- 400 and 300 MHz NMRs, with auto-samplers and variable temperature.
- Multi-ion Probe (H, F, C, N, P etc.)
- Multiple Agilent 1100 HPLC units.
- Five Prep HPLC systems including ELSD and reverse-phase prep capability.
- Polarimeter.
- FT-IR.
- Two walk-up LC/MS spectrometers.
- GC system.
- KF Titrator.
- Access to CHN, ROI, LOD, Exact Mass..
- Electronic Notebook System.
New c-GMP capabilities

- **Phase 1: Completed 4Q2019**
  - First line of wet chemistry
    - ✓ 30 L (2) mobile reactors per line with walk-in hoods for up to 10 kg output (chemistry dependent)
    - ✓ Temp ranges should be -40 C to 240 C
    - ✓ OEB 4 Ready

- **Phase 2: On Hold**
  - Second line of wet chemistry
    - ✓ 5L (1) & 10L (1) mobile reactors per line with walk-in hoods for up to 3 kg output (chemistry dependent)
    - ✓ Temp ranges should be -40 C to 240 C

Both labs will have access to finishing area for drying and to QC lab. Each GMP unit will be validated internally with “next in line” Dipharma projects followed by FDA visit.
Kalamazoo cGMP Photos
Kalamazoo cGMP Photos
Kalamazoo cGMP Photos
Kalamazoo cGMP Photos
Kalamazoo cGMP Photos
Kalamazoo cGMP Photos
Dipharma Francis’s R&D team

More than 40 researchers…

- Creative, and talented BSc or PhD researchers
- Sound background in synthetic organic chemistry
- Analytical team focused on method development, product and related impurities characterization
- Good know how and deep knowledge in API solid state and polymorphism

Researchers of R&D Centre in Milan
Dipharma R&D Tools

- HPLC and UPLC
- HPLC-MS/Triple Quadrupole and Ion Trap
- GC and GC-MS
- ICP-MS
- NMR
- XRPD
- Lab miller
- Lab micronizer
- Particle-size analyzer (Malvern)
- Reaction Calorimeter
- DSC
- Spray Dryer
- Turbidimeter Crystal 16® for crystallization screening
- Pre-formulation Lab (dissolution test apparatus, blender, tablet press etc.)
Dipharma Group, your unique provider

- Preclinical
- Phase I
- Phase II
- Phase III
- Commercial

No GMP
Simplified GMP
Full GMP
Dedicated teams to support each CS project

- Project Manager/Lead Chemist
- Development Team
- GMP Operators
- QC/QA
- RA support
## Dipharma cGMP Pilot plants

<table>
<thead>
<tr>
<th></th>
<th>Caronno (Small Production Plant)</th>
<th>Mereto (New Pilot Plant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Reactor Volume</td>
<td>11800 l</td>
<td>2100 l</td>
</tr>
<tr>
<td>Operating temperature range</td>
<td>-15°C to +180°C</td>
<td>-80°C to 200°C</td>
</tr>
<tr>
<td>Reactor volume</td>
<td>130 to 3,000 l</td>
<td>250 to 1,000 l</td>
</tr>
<tr>
<td>Max Pressure</td>
<td>Up to 6 bar (standard equipment)</td>
<td>Up to 6 bar Up to 40 bar Biazzi Hydrogenator</td>
</tr>
</tbody>
</table>
### Dipharma cGMP Production plants

<table>
<thead>
<tr>
<th></th>
<th>Mereto</th>
<th>Baranzate</th>
<th>Caronno</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Reactor Volume</strong></td>
<td>200,000 l</td>
<td>90,000 l</td>
<td>230,000 l</td>
</tr>
<tr>
<td><strong>Operating temperature range</strong></td>
<td>-10°C to 280°C</td>
<td>-20°C to 150°C</td>
<td>-15°C to +180°C</td>
</tr>
<tr>
<td><strong>Reactor volume</strong></td>
<td>1,000 to 10,000 l</td>
<td>500 to 12,000 l</td>
<td>800 to 12,000 l</td>
</tr>
<tr>
<td><strong>Max Pressure</strong></td>
<td>Up to 6 bar (standard equipment)</td>
<td>Up to 5 bar (standard equipment)</td>
<td>Up to 5 bar</td>
</tr>
<tr>
<td></td>
<td>Up to 40 bar Biazzi Hydrogenator</td>
<td></td>
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</table>
Why Dipharma for your CS project?

Together with a sound technical skill, Dipharma Group offers a strong and reliable support for projects, ranging from pre-clinical lab scale preparations up to full industrial, multiple tons manufacturing production.

Along with process design and technical improvement, we provide our strong commitment in reaching a cost competitive solution, in order to turn a bright idea in a successful commercial opportunity.
Our History, values and performances give Dipharma Group a solid background to support Custom Synthesis projects including:

- Process design and feasibility
- Process impurity identification and synthesis
- Process development and improvement
- Safety assessment and Calorimetric study
- Analytical development
- Solid state characterization
- Pre formulation evaluation
Contents

1. Who is Dipharma Group
2. Why Dipharma Group for your custom synthesis project?
3. Core technologies: challenging chemistry
Core technologies: challenging chemistry

- Handling of explosives
- Nitroesters
- Nitration of aromatic rings
- Handling of nitroalkanes
- Azide Chemistry
- Hydrazine Chemistry
- Hydroxylamine Chemistry
- Chlorine Chemistry
- Carbohydrate Chemistry
- Hydrogenations (Biauzzi technology)
- Enzymatic Chemistry
- Chiral products
- Organometallic Chemistry
Handling of explosives

Not only knowledge and experience in handling explosive compounds, but also in-house equipment to measure explosive properties of materials

- Koenen test
- Fall hammer test
- Friction test
Nitroesters are molecules with a high energy content which can decompose explosively if not appropriately handled.

Industrial Application: Nitroglycerin and ISDN (full industrial scale)

References: Process to manufacture BDMN, a key intermediate in NONaproxen: Castaldi et al: US 7,335,789 US 7,851,649
Process for the purification of 1,4-butanediol mononitrate: Scubla et al. US 7,947,855
Nitration of aromatic rings

Exothermic and potentially dangerous reactions which require know-how and safety evaluations

Industrial Application: Entacapone (full industrial scale)

References: Process to manufacture Varenicline with a double nitration: Attolino E., Rossi R., Allegrini P. EP 2 551 269
Nitroalkanes are very versatile intermediates in organic synthesis and can be used in a number of ways.

**Industrial Application:** Telaprevir, Linezolid

**References:**
- Process to Linezolid with an asymmetric Henry reaction: Colombo L. et al EP2072505
- Process to Telaprevir intermediate with a Michael type reaction: Iuliano A., et al EP2801566
Azides are compounds containing a -N₃ group which are hazardous because they can decompose, generating nitrogen gas.

Azides used at industrial scale: NaN₃, DPPA, Me₃SiN₃, Oct₃SnN₃

Main applications: preparation of Tetrazoles and Curtius reaction

**Industrial Applications:** Sartans, Cilostazol, Rufinamide (full industrial scale)

**References:** Method for the preparation of rufinamide: Attolino et al.: US 8,198,459
Process for preparing Cilostazol Beltrame et al.: EP 1 660 480
Hydrazine Chemistry: Wolff-Kishner reduction

The Wolff-Kishner reduction is an organic reaction used to convert an aldehyde or ketone to an alkane using hydrazine, generating nitrogen gas.

Industrial Applications: Ursodeoxycholic acid (WW leading manufacturer)
Hydroxylamine, dangerous to handle because explosive when dry, can be used in many ways in organic synthesis. For example, it can be used to functionalize carbonyl groups.

\[
\text{R}^\text{R'} \text{O} \xrightarrow{\text{NH}_2\text{OH}} \text{R}^\text{R'} \text{N} \text{OH}
\]

**Industrial Application:** Zonisamide, Zileuton

**References:**


Even though chlorine is a toxic and hazardous gas, chlorination reactions allow to obtain versatile intermediates which can be used in a variety of ways.

**Industrial Application:** C.M. GMP intermediate
(Several Tons/year)
Carbohydrate Chemistry

Sugar chemistry allows to synthesize poly hydroxylated compounds with defined stereogenic centers but requires a specific know-how because of the very peculiar reactivity of carbohydrates.

For example, diastereoselective double reductive aminations.

Industrial Application: Miglustat and Migalastat

References: Process to Miglustat: Malvestiti, A.; Brunoldi, E.; Attolino, E. US9708263
Hydrogenation typically constitutes the addition of pairs hydrogen atoms to a molecule, generally in the presence of a catalyst. Even though hydrogen gas is dangerous to handle, many different functional groups can be hydrogenated, making hydrogenation a versatile synthetic tool.

Industrial Application: Venlafaxine, Benazepril

References: Process to manufacture Benazepril: Castaldi G., Mantegazza S., Razzetti G., WO2003092698
Enzymatic reactions can be highly enantioselective, specific, clean reactions which can be carried out in mild conditions.

**Industrial Application:** Pramipexole, Fosinopril (Industrial scale)

**References:**
- Process to manufacture Pramipexole: Riva, S. et al US 7662610
**Classic resolutions**
The desired enantiomer is isolated by forming a diasteromeric salt

**Enzymatic resolutions**
As shown in the previous slide, an enzyme is used to hydrolize only one enantiomer

**Industrial Application:** Telaprevir

**References:**
Processes to Telaprevir intermediate
Taddei M.; Attolino, E.; Balducci E.; Michieletti M.; WO 2013120871 and
Attolino, E.; Bove A.; Brunoldi E.; Allegrini P. WO 2013136265
Asymmetric synthesis
Asymmetric synthesis allows to synthetise only the desired enantiomer of a product, with a much higher atom economy and less byproducts to be reworked.

For example, enantioselective oxidation of sulphur

![Chemical structure](image)

**Industrial Application:** Dexlansoprazole (Validated industrial process)

**References:** Process to manufacture Dexlansoprazole: Attolino, E.; Lucchini V. US 8198455.
Organometallic chemistry involves chemical bonds between carbon atoms and a metal atom. The metal-carbon bond has special characteristics which can be used in many different ways.

**Hexyl-lithium**

**Industrial Application:** Tolterodine

**References:** Razzetti G. et al EP 1 693 361

**Grignard reagents**

**Industrial Application:** Telmisartan

**References:** Allegrini P. et al.. EP 1719766

**Magnesium diisopropylamide**

**Industrial Application:** Sartans

**References:** Castaldi G. et al WO 2005014560
Sonogashira Cross Coupling

Industrial Application: Fexofenadine, Terbinafine, Vilazodone and Cinacalcet

References: Taddei, M. et al. US2014275542

Negishi Cross Coupling

Industrial Application: Irbesartan, Losartan

References: Castaldi G. et al. WO 2005014560

Suzuki Cross Coupling

Industrial Application: Valsartan

References: Verardo G. et al. EP 1533305
Thanks for your attention