Since 1949 Dipharma

Better Together.

Kalexsyn
a Dipharma Francis S.r.l. company

Challenging chemistry requires a skilled partner

Updated as of April 15, 2020

Contents

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2 Our R&D Team & Tools

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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
experienceininnovation
in handling complex
and hazardous
chemical processes safely

Dipharma Since 1949

* 2018, *not audited data*

Kalexsyn
a Dipharma Francis S.r.l. company

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

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Headquarters Commercial Offices R&D Laboratories

Kalexsyn
a Dipharma Francis S.r.l. company

cGMP production sites

Baranzate, Milan
Dipharma Francis S.r.l.

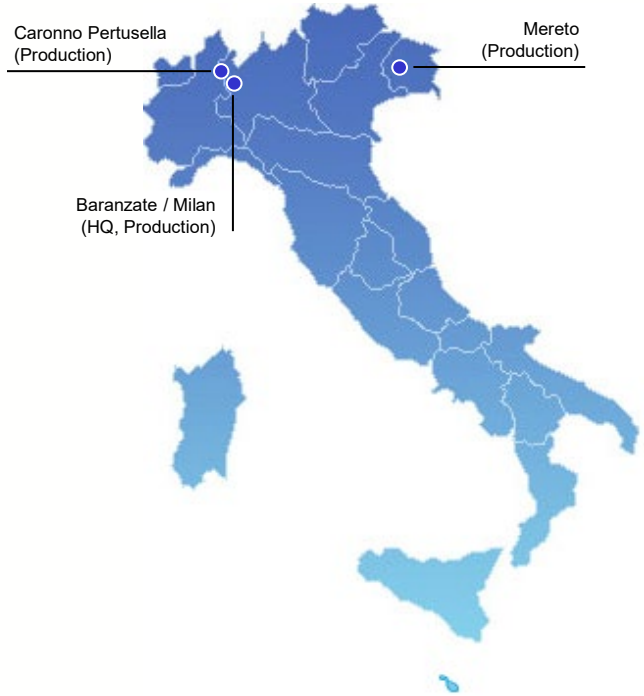
FDA inspected since 1970

Caronno, Varese
Dipharma Francis S.r.l.

FDA inspected since 1978

Mereto, Udine
Dipharma Francis S.r.l.

FDA inspected since 1980



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R&D and cGMP* in the United States
Kalexsyn

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

Kalexsyn, Inc.
Kalamazoo, MI

Founded in 2003

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*cGMP 1Q2020, Commercial Certified

GMP Compliance Status

Dipharma Francis Baranzate, Milan
First FDA inspection: 1970

YEAR	AUTHORITY
1970	FDA
1973	Italian MoH
1975	FDA
1977	FDA
1979	FDA
1980	Italian MoH
1980	FDA
1983	FDA
1986	FDA
1987	Italian MoH
1989	FDA
1990	FDA
1992	Italian MoH
1994	FDA
1997	Italian MoH
1997	FDA
1999	FDA
2002	FDA
2003	AIFA
2005	FDA
2005	AIFA
2009	FDA
2009	AIFA
2012	FDA
2012	AIFA
2015	FDA
2015	AIFA
2016	AIFA
2017	Italian MOH (vet. drugs)
2017	FDA*
2018	AIFA

Dipharma Francis Caronno
First FDA inspection: 1978

YEAR	AUTHORITY
1971	Italian MoH
1978	FDA
1980	FDA
1981	FDA
1983	FDA
1984	Italian MoH
1985	FDA
1987	FDA
1990	Italian MoH
1992	FDA
1994	Italian MoH
1997	FDA
2003	FDA
2004	AIFA
2007	AIFA
2007	FDA
2010	FDA
2010	AIFA
2012	FDA
2013	AIFA
2016	FDA
2016	AIFA
2018	AIFA
2019	AIFA

Dipharma Francis Mereto
First FDA inspection: 1980

YEAR	AUTHORITY
1980	FDA
1980	Italian MoH
1983	FDA
1985	Italian MoH
1986	FDA
1990	Italian MoH
1990	FDA
1996	FDA
1998	Italian MoH
1999	FDA
2004	AIFA
2004	FDA
2007	AIFA
2010	AIFA
2010	FDA
2013	AIFA*
2013	AIFA
2014	FDA
2015	AIFA
2015	AIFA*
2017	FDA
2017	PMDA
2018	AIFA

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* AIFA inspection for manufacturing of Pharma Mixtures

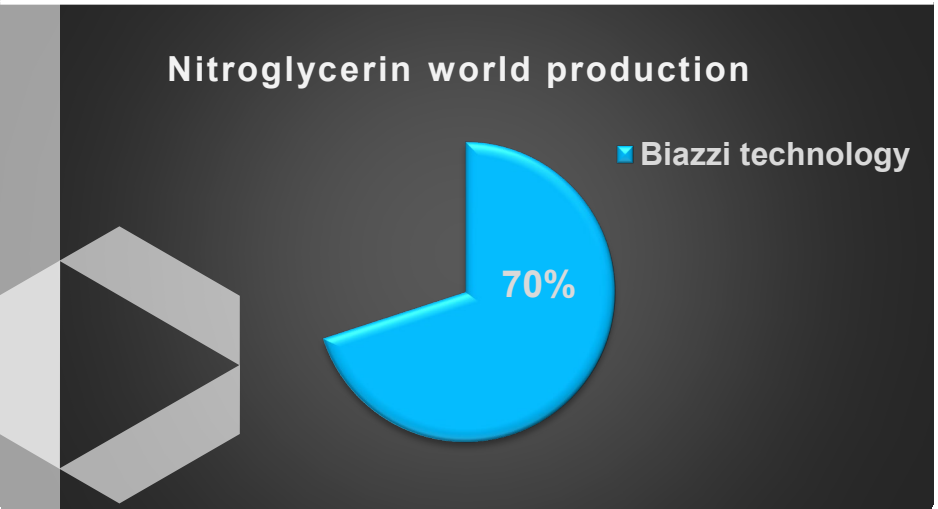
* Mutual Recognition Agreement

Mario Biazzi
(1897-1974)

Our history

experienceininnovation

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

70 years Since 1949


35R2
35R3
35R4
35R5
35R6
V74
V88

Our Values

Safety

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

Innovation

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

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

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

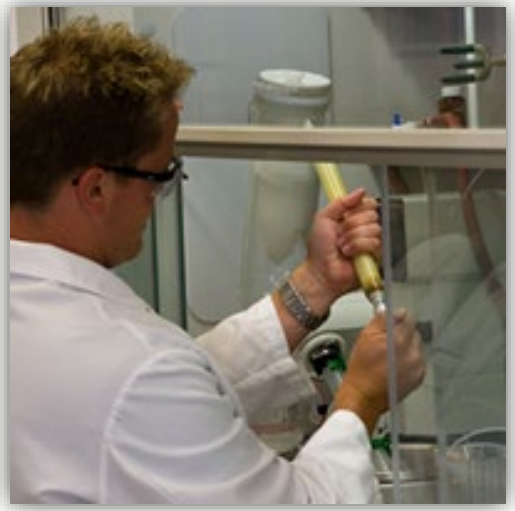
Ethics

- Loyal customers
- Loyal employees
- Loyal shareholders

USA R&D Team

Kalexsyn

- 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.



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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.

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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.

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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.

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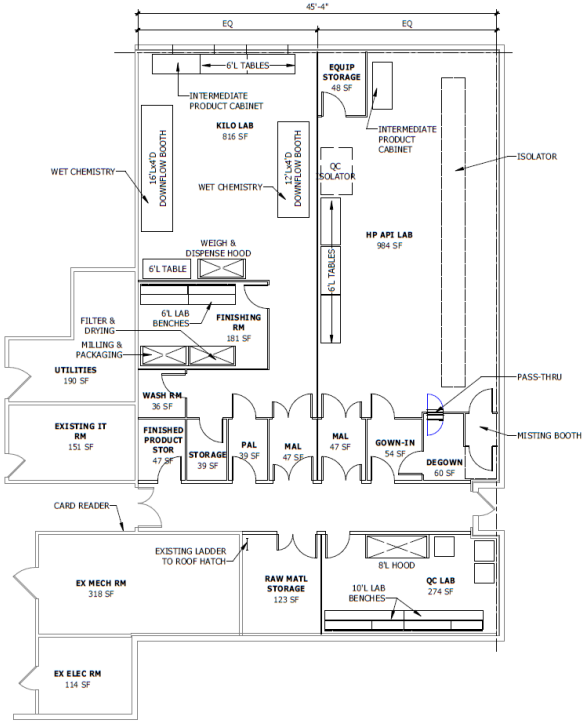
New c-GMP capabilities

- 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 hooc 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.



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Kalamazoo cGMP Photos

Since 1949 Dipharma

Kalamazoo cGMP Photos

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Kalamazoo cGMP Photos

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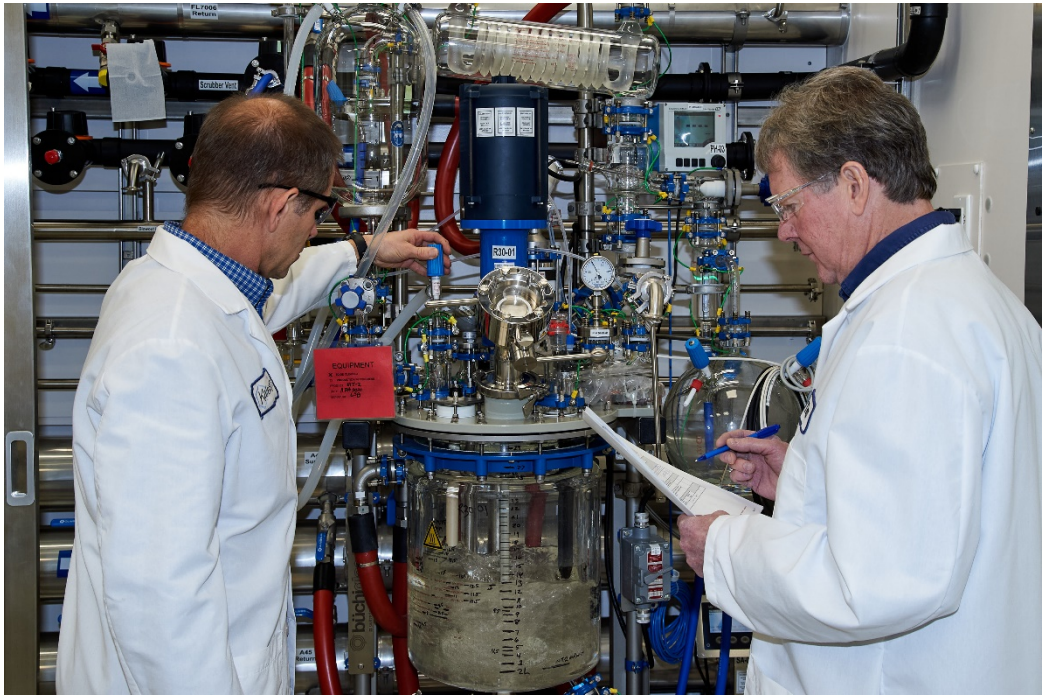
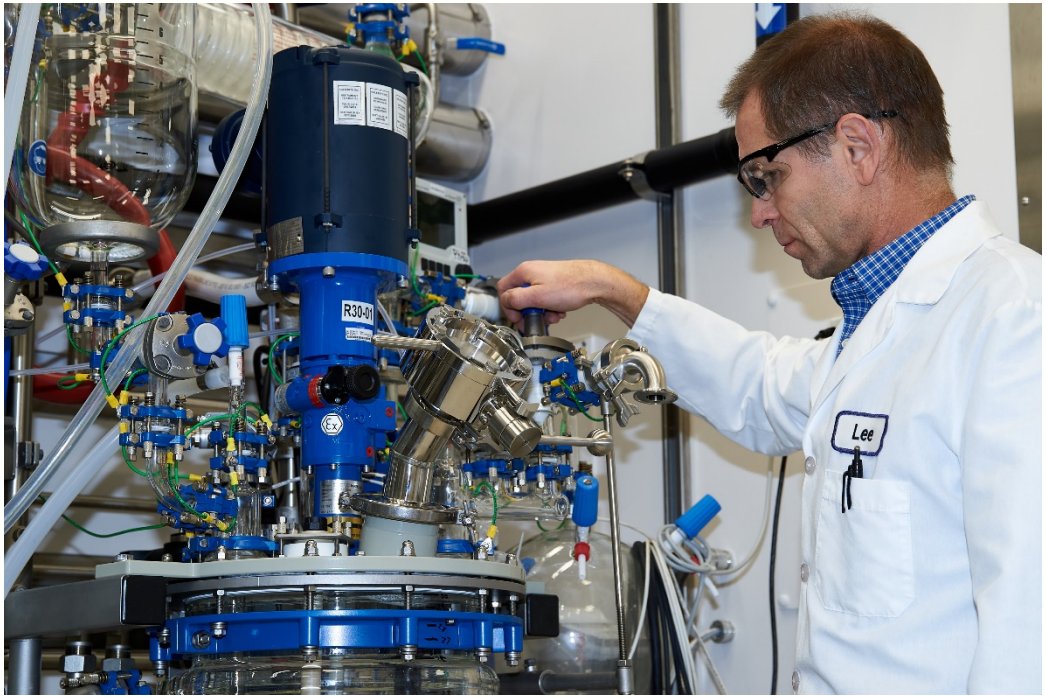
Kalamazoo cGMP Photos



Since 1949 Dipharma

Kalamazoo cGMP Photos

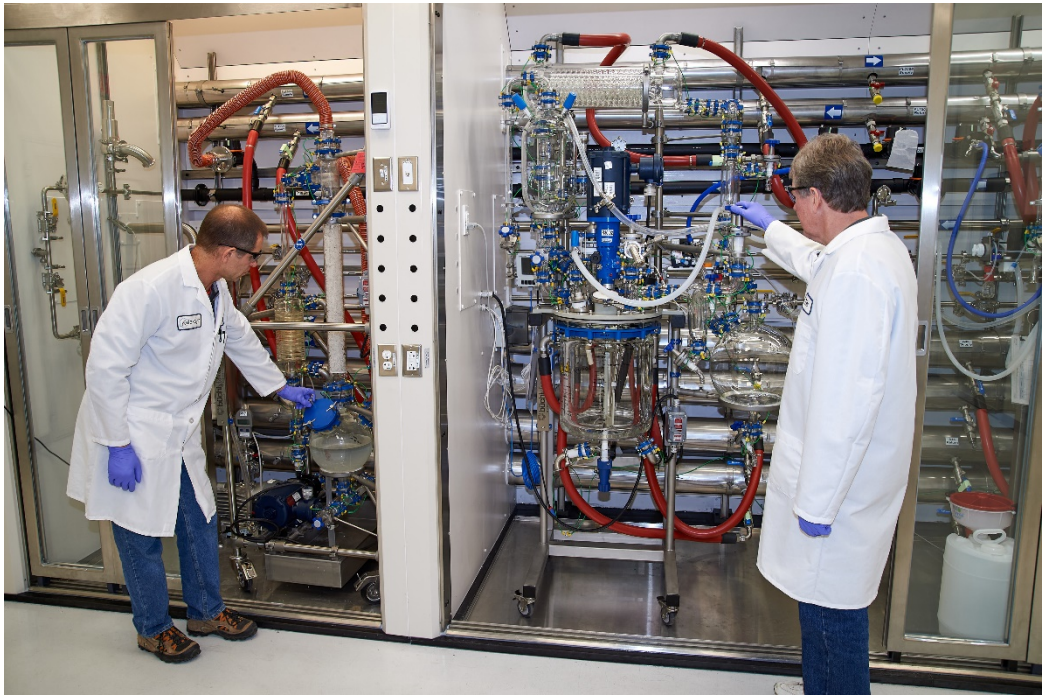


Since 1949 Dipharma

Kalamazoo cGMP Photos

Since 1949 Dipharma

Kalamazoo cGMP Photos



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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

Dipharma Since 1949

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.)

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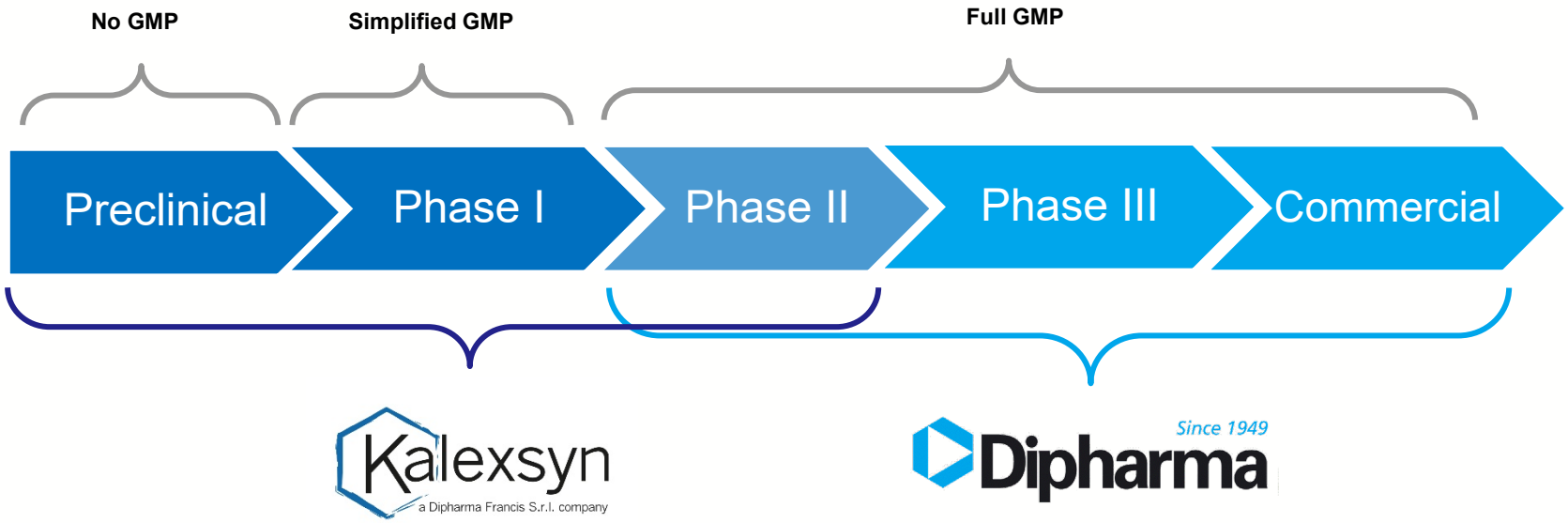
Dipharma Group, your unique provider



Dedicated teams to support each CS project

- Project Manager/Lead Chemist
- Development Team
- GMP Operators
- QC/QA
- RA support

Dipharma cGMP Pilot plants

	Caronno (Small Production Plant)	Mereto (New Pilot Plant)
Total Reactor Volume	11800 l	2100 l
Operating temperature range	-15°C to +180°C	-80°C to 200°C
Reactor volume	130 to 3,000 l	250 to 1,000 l
Max Pressure	Up to 6 bar	Up to 6 bar (standard equipment) Up to 40 bar Biazzi Hydrogenator

Dipharma cGMP Production plants

	Mereto	Baranzate	Caronno
Total Reactor Volume	200,000 l	90,000 l	230,000 l
Operating temperature range	-10°C to 280°C	-20°C to 150°C	-15°C to +180°C
Reactor volume	1,000 to 10,000 l	500 to 12,000 l	800 to 12,000 l
Max Pressure	Up to 6 bar (standard equipment) Up to 40 bar Biazzi Hydrogenator	Up to 5 bar (standard equipment)	Up to 5 bar

Why Dipharma for your CS project?

Together with a sound technical skill, Dipharma Group offers a strong and relialable 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 committment in reaching a cost competitive solution, in order to turn a bright idea in a successfull commercial opportunity.

Why Dipharma for your CS project?

Our History, values and performances give Dipharma Group a solid backgound 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

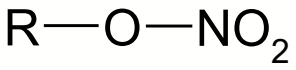
- Handling of explosives
- Nitroesters
- Nitration of aromatic rings
- Handling of nitroalkanes
- Azide Chemistry
- Hydrazine Chemistry
- Hydroxylamine Chemistry
- Chlorine Chemistry
- Carbohydrate Chemistry
- Hydrogenations (Biazzi technology)
- Enzymatic Chemistry
- Chiral products
- Organometallic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

Handling of explosives

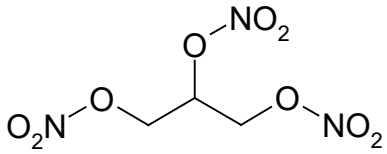
Not only knowledge and experience in handling explosive compounds,
but also in-house equipment to measure explosive properties of materials

- Koenen test
- Fall hammer test
- Friction test

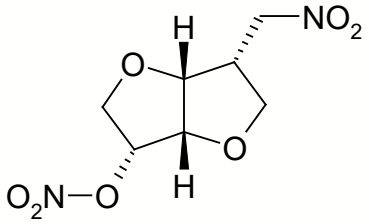
Nitroesters



Nitroesters are molecules with a high energy content which can decompose explosively if not appropriately handled



Nitroglycerin



ISDN

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

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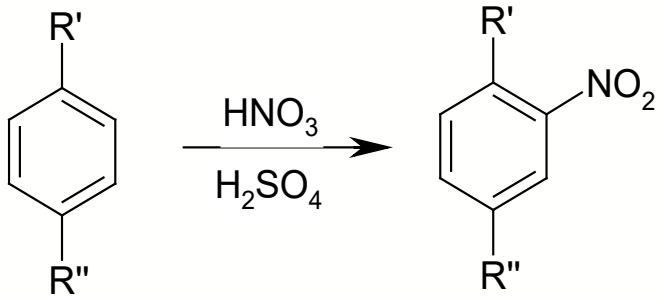
Nitration of aromatic rings

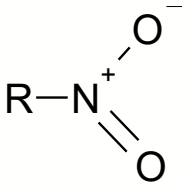
Exothermic and potentially dangerous reactions which require know-how and safety evaluations



Industrial Application: Entacapone
(full industrial scale)

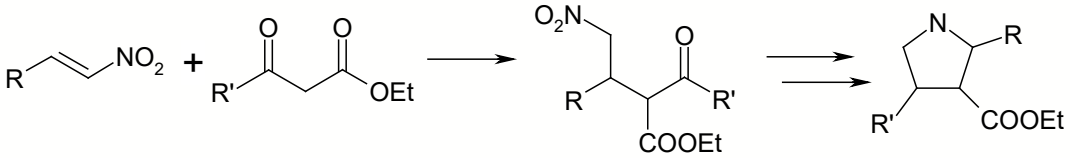
References: Process to manufacture Varenicline with a double nitration:
Attolino E., Rossi R., Allegrini P. EP 2 551 269

Nitroalkanes

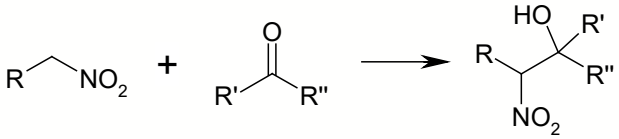


Nitroalkanes are very versatile intermediates in organic synthesis and can be used in a number of ways

Micheal-type additions



Henry reaction



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

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Azide Chemistry

Azides are compounds containing a $-N_3$ group which are hazardous because they can decompose, generating nitrogen gas

Azides used at industrial scale: NaN_3, DPPA, Me_3SiN_3, Oct_3SnN_3

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

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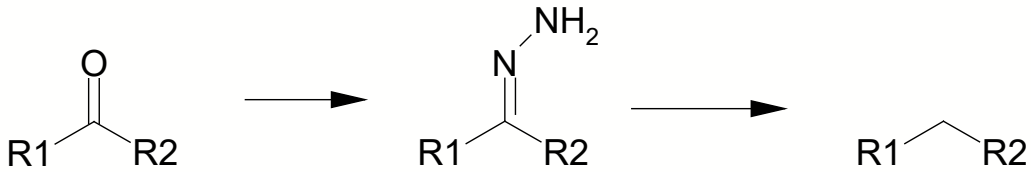
Hydrazine Chemistry: Wolf-Kishner reduction

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)

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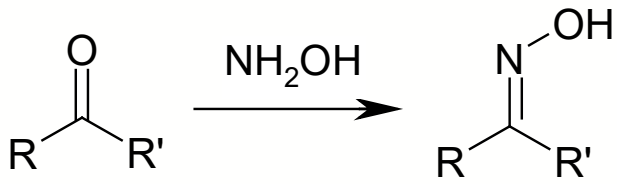
Hydroxylamine Chemistry

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

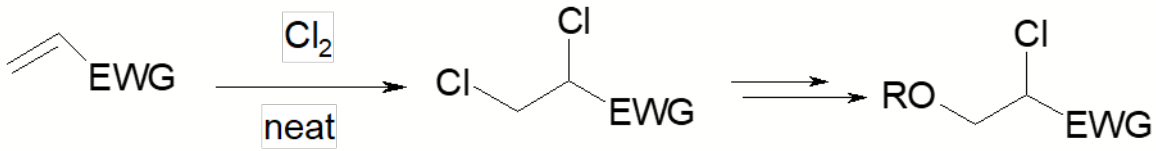


Industrial Application: Zonisamide, Zileuton

References: Smart process to manufacture Zonisamide: Allegrini P., Bologna A., Castaldi G., Lucchini V., Mantegazza S., Razzetti G., WO2004063173 A1
Process to manufacture Zileuton: Attolino, E.; Dell'Anna, G.; Rossi, R.; Allegrini, P.; Razzetti, G. US 2009/0286996.

Chlorine Chemistry

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

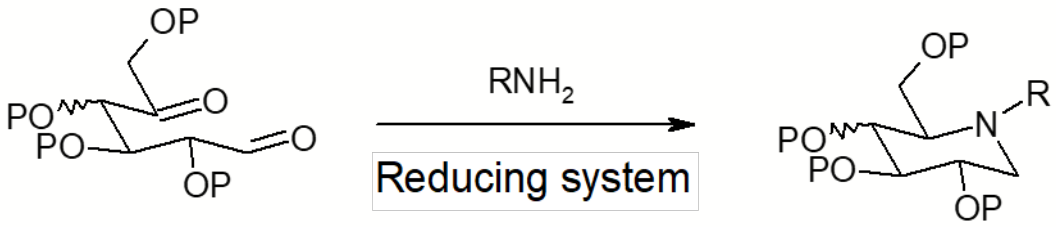


Industrial Application: C.M. GMP intermediate (Several Tons/year)

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

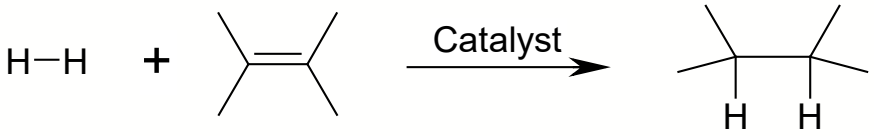


Industrial Application: Miglustat and Migalastat

References: Process to Miglustat :Malvestiti, A.; Brunoldi, E.; Attolino, E. US9708263

Hydrogenations

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

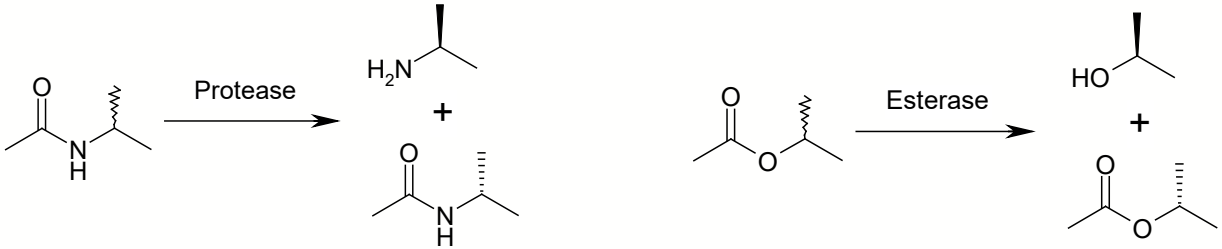


Industrial Application: Venlafaxine, Benazepril

References: Process to manufacture Benazepril: Castaldi G., Mantegazza S., Razzetti G., WO2003092698

Enzymatic Chemistry

Enzimatic 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
Process to Fosinopril key intermediate : Razzetti G., et al. EP 2264039 and US 8097724

Chiral products

Classic resolutions

The desidered enantioner is isolated by forming a diasteromeric salt

Enzymatic resolutions

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

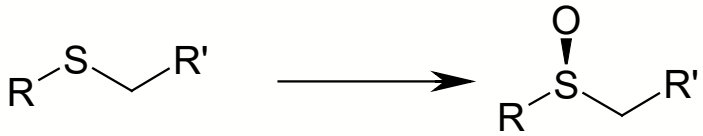
Industrial Application: Telaprevir

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



Industrial Application: Dexlansoprazole (Validated industrial process)

References: Process to manufacture Dexlansoprazole: Attolino, E.; Lucchini V. US 8198455.

Organometallic Chemistry

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

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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 alWO 2005014560

Suzuki Cross Coupling

Industrial Application: Valsartan

References: Verardo G. et al. EP 1533305

Thanks for your attention