

# SIMS

“Long Tradition Meets Strong Technology”



**S.I.M.S.**  
*Società Italiana Medicinali Scandicci*  
STABILIMENTI CHIMICO - FARMACEUTICI INDUSTRIALI  
*Società a responsabilità limitata - Capitale interamente versato L. 5.000.000.000*  
Stabilimento e Amministrazione: Loc. Filarone - 50066 REGGELLO (FI)  
Sede legale: Via Dante Da Castiglione, 8 - 50125 Firenze  
Codice Fiscale/Partita I.V.A./VAT Number: IT 03076410483  
P.O. BOX 390 - 50100 FIRENZE - FAX 055.863008 - Telefoni 055.863051 - 3 linee - <http://www.rangcri.it/sims> - e-mail: [sims@rangcri.it](mailto:sims@rangcri.it) - C/C Postale 11536505 - C.C.I.A.A. Firenze 269040 - Iscr. Trib. Firenze N. 30620  
OUR BANKERS: - BANCA TOSCANA - Figline Valdarno Branch - Account Nr. 7272.51 - BANCA NAZIONALE DEL LAVORO - Florence Head Office - Account Nr. 16392





<https://youtu.be/HuMUn6x64Gg>

# SIMS

## Our CDMO Services

With over 85 years of experience in Fine Chemicals, our chemical toolbox is different from most providers.

Hazardous reactions under cGMP are our daily business. With our skills in API life cycle management and a sound list of APIs, we use this know-how for your products. Family owned, we make fast decisions and are totally customer oriented.



# History

1937

Founded by Ugo Rangoni, plant in Scandicci  
focus development and production of generic APIs

1972

First US DMF filed

1973

Niccolò Rangoni (son) takes lead

1974

New and actual site opened in Reggello

1980's

CDMO services with multinational pharma  
New Drying Facility

1996

New incineration plant for solid and liquid waste

2010

New API finishing suites

2016

PMDA Certification

2020

Latest US FDA & AIFA Inspections (2024)  
Since 2017 MRA between US FDA and AIFA, Italy

2024

New Photovoltaic Solar Plant



# THE RANGONI GROUP

RANGONI S.R.L.  
GROUP HOLDING  
Florence, Italy

SORELLE  
FIORENTINE  
S.R.L.

Footwear  
Production

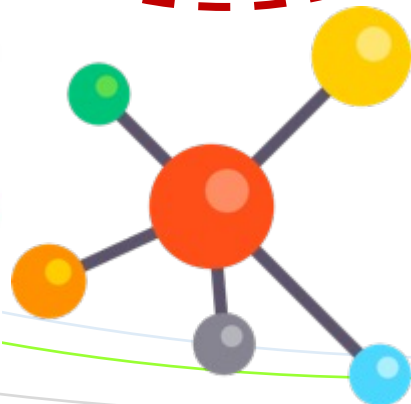


RANGONI  
AMERICA

Retail & Wholesale  
footwear  
distribution



S.I.M.S.  
S.R.L.



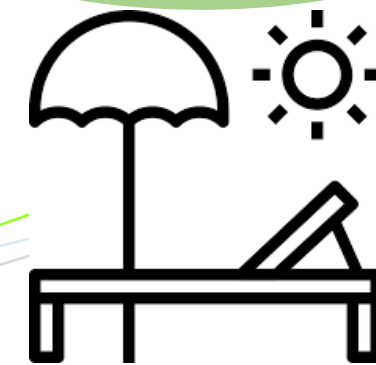
SACIP SAS

Real Estate



MINIERE DI  
FIZZANO

Beach Club



AZIENDA  
AGRICOLA  
LE FALLE

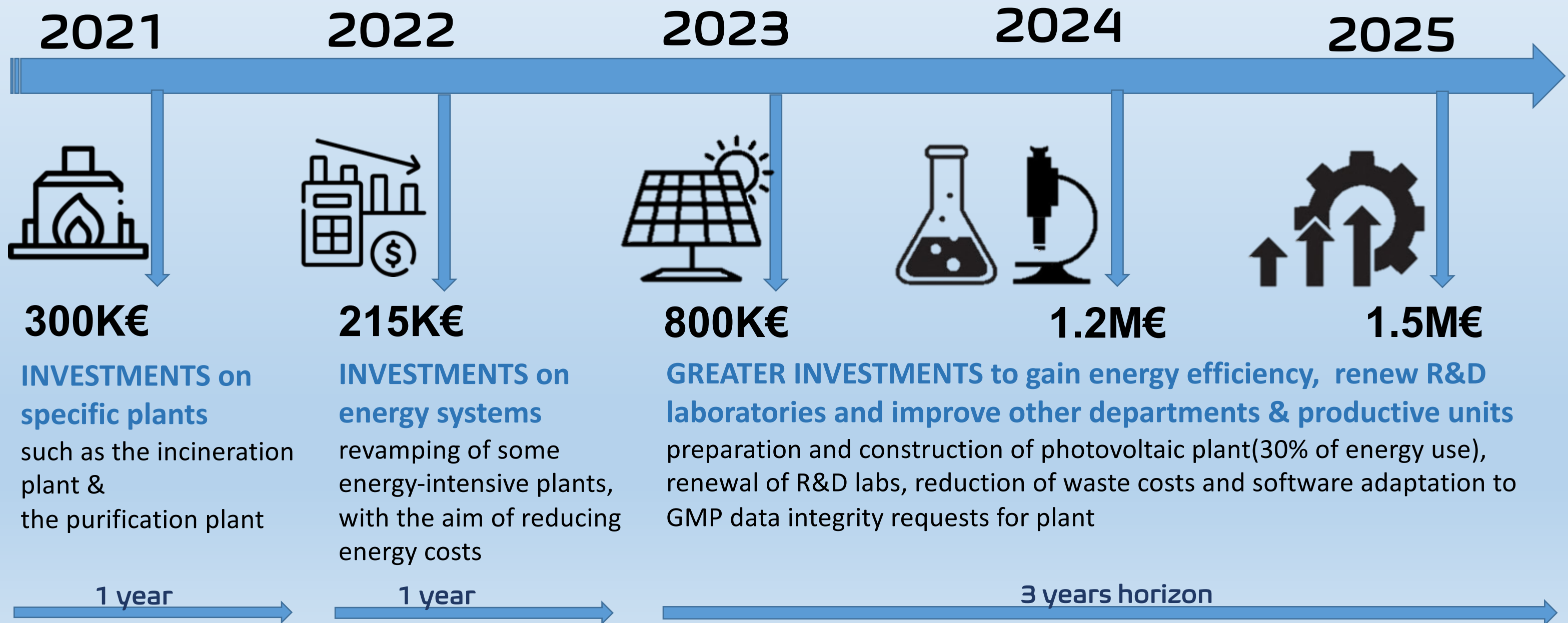
Wine & Oil  
Production



# SIMS INVESTMENTS OVERVIEW



5 years goals:  
energy efficiency, new laboratories , new technologies,  
sustainability, growth



# 1st Phase of a New Photovoltaic Plant 2024 on stream



Generates about 20-25% energy needs  
2nd phase planned for 2025/26

# Strengths

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- Our experience from generic API development serves to optimize COGS for Exclusive Products
- Hazardous Reactions or Energetic Chemistry
- 280 m<sup>3</sup> of Total Reactor Capacity in 3 plants
- Injectable APIs

**Our Strength: Hazardous Processes under GMP**



# LOCATION

Located 30 km  
Southeast of Florence,  
Italy

Opened in  
1974, operation was  
moved from the original  
site

**By train:**

Fast train 300 km/hr from  
Milan Central Station 2 hours

Local train from Florence Main  
Station to Rignano sull'Arno in  
30 minutes

**By car:**

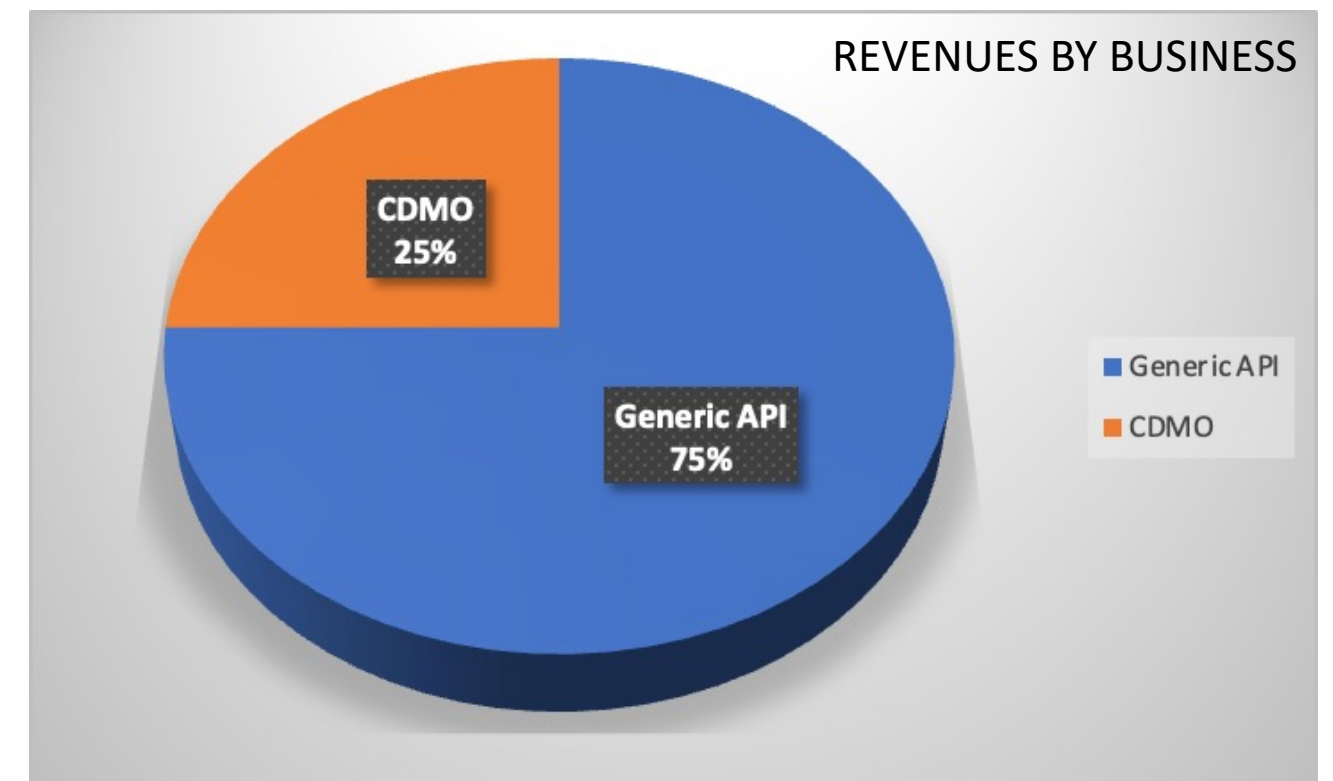
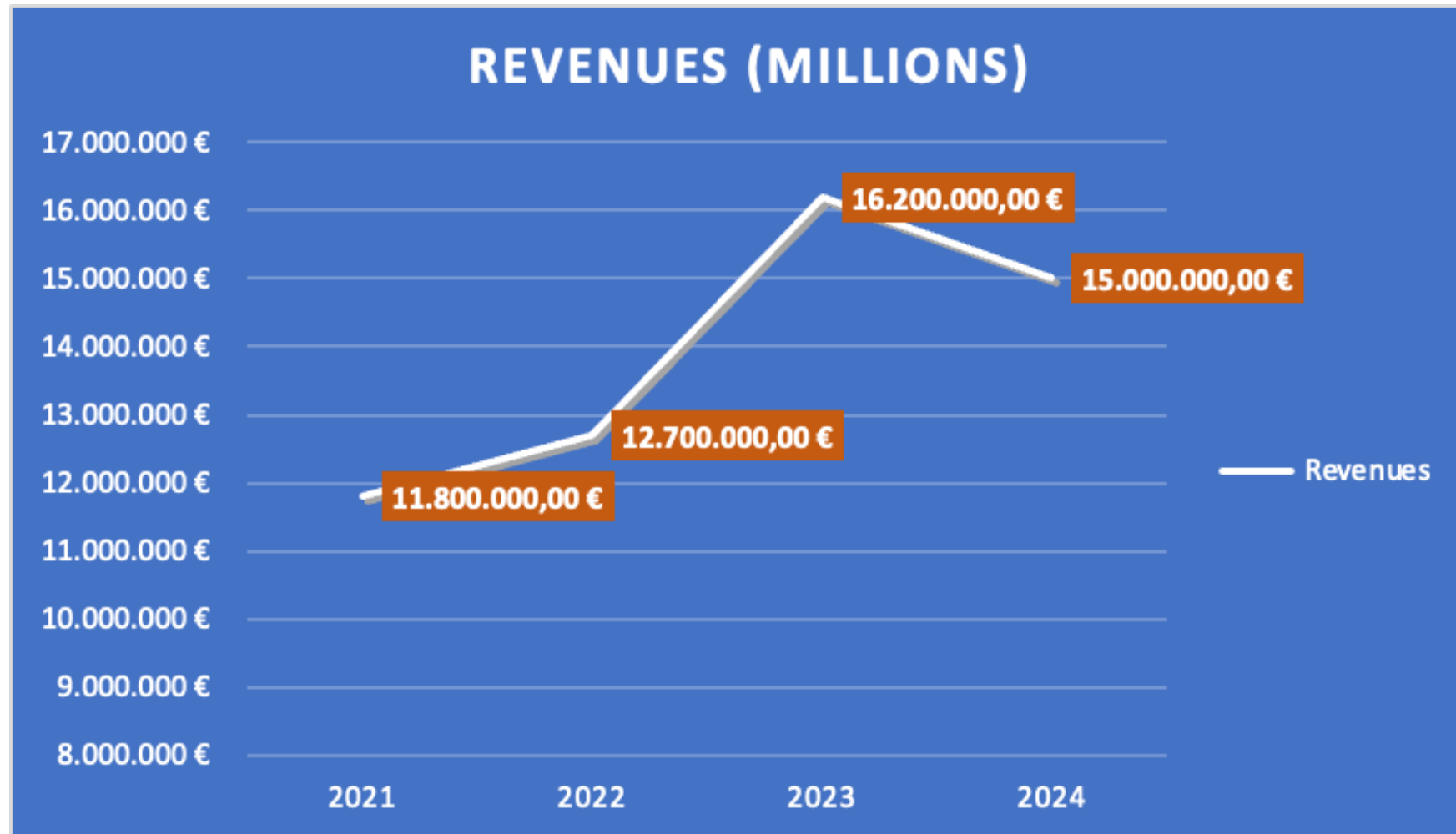
30 min from the airport  
25 min from central Florence

**By flight:**

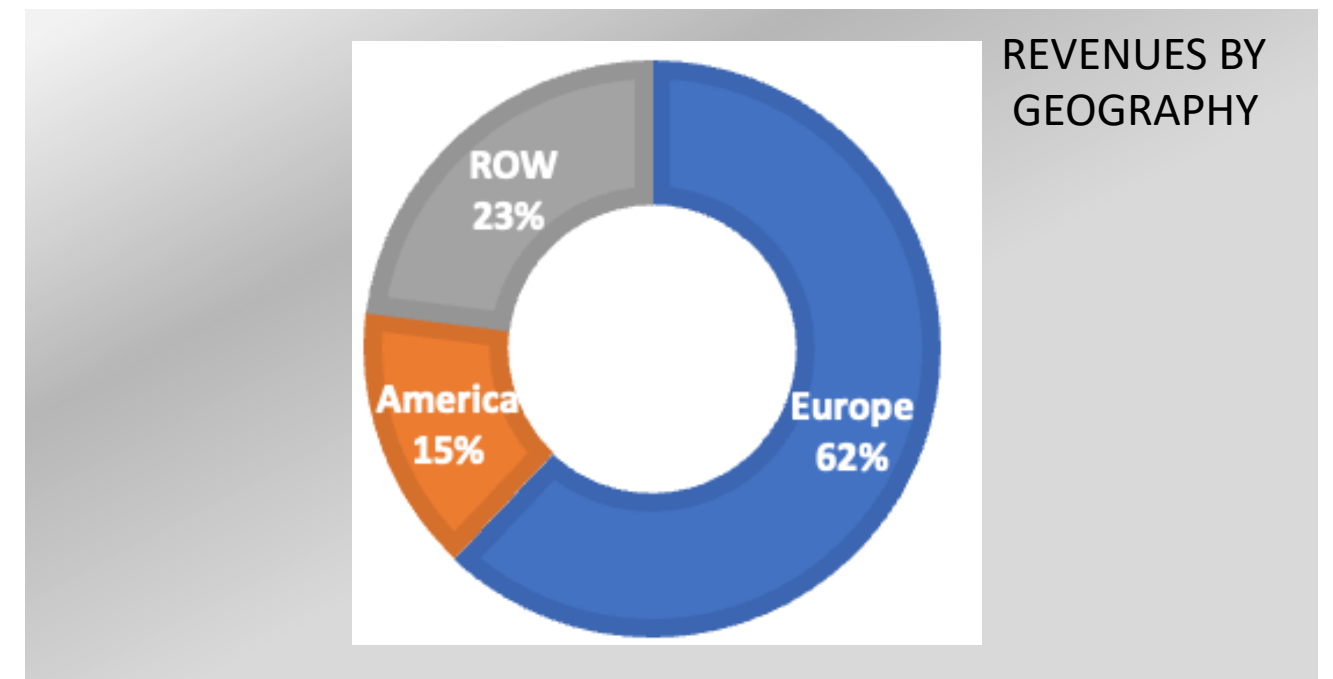
From any main airport in  
Europe to Florence Airport



# KEY FIGURES



109 Employees  
(15% with chemical degree)



# ORG CHART



# PEOPLE

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## 109 Employees (15% with chemical degree)

DEPARTMENT	NUMBER
Sales & Marketing	3
Administration	5
Technical Office	2
EHS	2
Maintenance	8
Quality Control	10
Quality Assurance	3
Regulatory Affairs	3
Research & Development *	6
Production	68

\* 5 graduated

**Our Strength: Scientific Expert and Stable Staff**

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# R&D: Synthesis and Analytical Development

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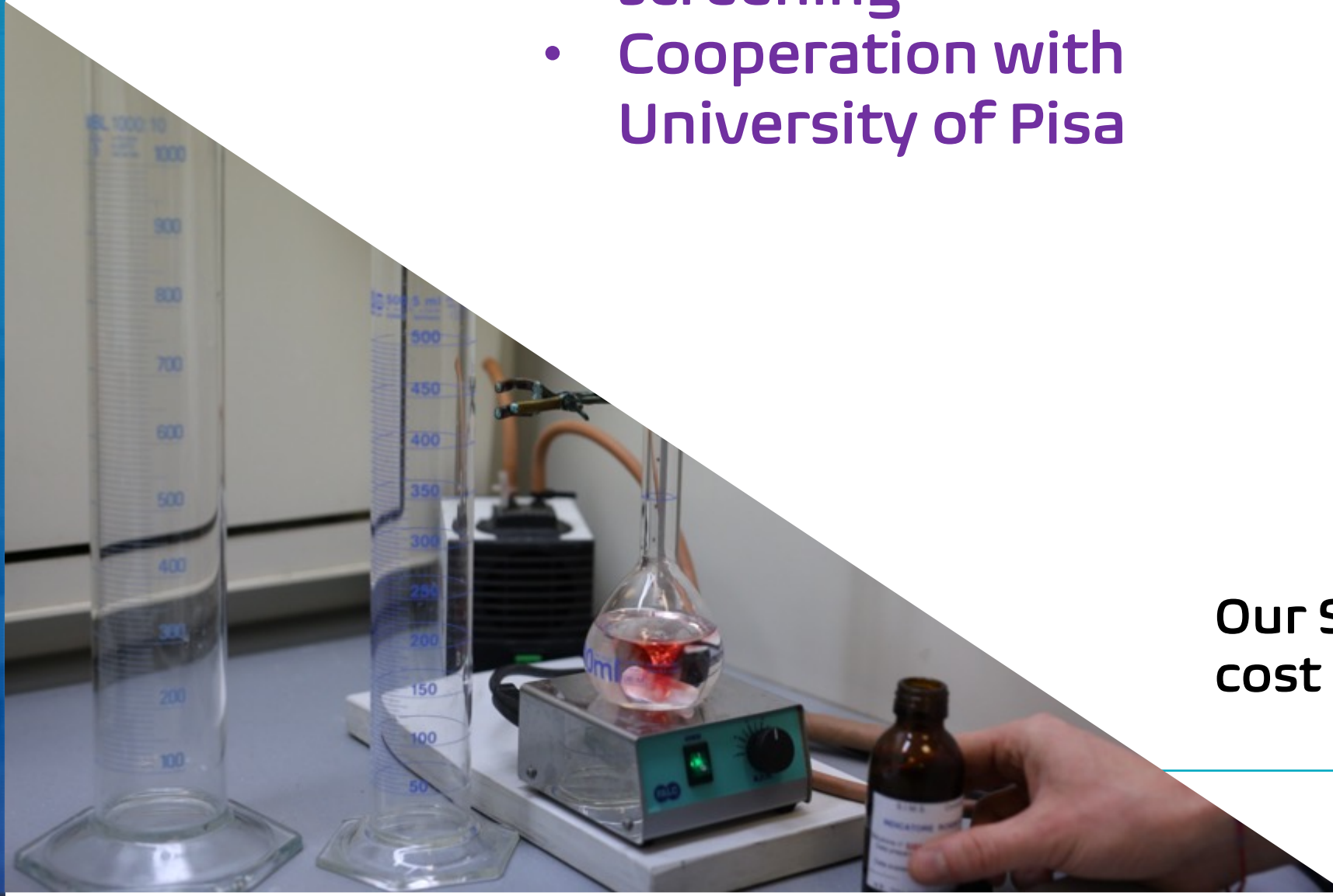
## Synthesis:

- Route Scouting
- Process R&D
- Crystalline form screening
- Cooperation with University of Pisa

## Analytical Development:

- HPLC
- GC
- IR
- UV
- Titration
- Polarimeters
- Granulometer
- Residual Humidity Ovens
- Melting Point
- NMR External
- MSGC External

**Our Strength: Expertise in developing cost competitive processes**



# SIMS collaborates with the Department of Chemistry of the University of Pisa for Research



UNIVERSITÀ  
DI PISA



# Quality Control

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- 10 Analysts
- 4 HPLC
- 4 GC
- 1 IR
- 1 UV
- 2 Titration
- 1 Polarimeter
- 1 Granulometer
- 3 Residual Humidity Ovens
- 2 Melting Point
- 2 Stability Chambers
- Data integrity System



## INSPECTIONS & CERTIFICATES LIST

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- Compliance with international cGMP
  - With US FDA Inspections since 1970'
  
  - AIFA Nov 2024
  - US FDA 2016
  - PMDA Japan 2020
  - AIFA Veterinary 2019
  
  - 20 Active DMFs/EDMFs
  - Number in Regulatory team: 3
  
  - Food Grade ingredients
  - Production of custom vitamin
  
  - Since 2017 Mutual Recognition Agreement between US FDA and AIFA, Italy
- 



***Our Strength:  
Extensive Regulatory  
History  
and Injectable API &  
Anesthetics***

# Environment Health & Safety

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- ✓ **EH&S** has represented a high priority at **SIMS** since the '70s
- ✓ First **Process Water Treatment** plant within the Italian industry (1974)
- ✓ **Incineration Unit for liquids and gases** including production steam (1996)
- ✓ **Cryogenic system** to treat chlorinated solvents
  - Reutilized as inert gas supply



## Health&Safety

- 👉 Integral part of process development system
- 👉 Continuous safety training

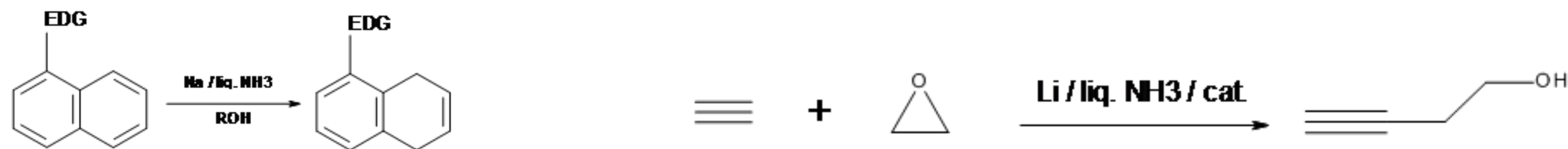


# Special Technologies

## Hazardous Reactor Systems - HIGHLIGHTS

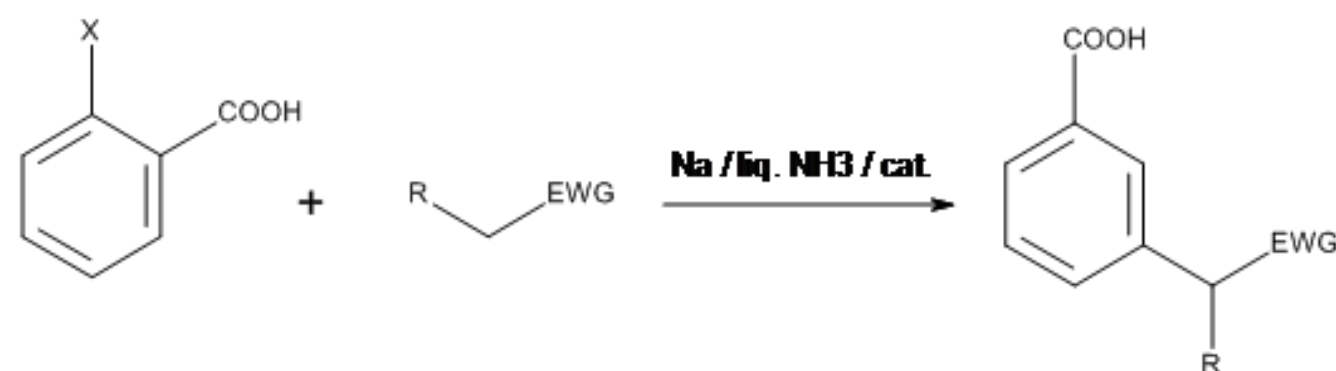
### ➤ Anhydrous Li or Na in liquid Ammonia

- 2 x 3500l and 1 x 4000l stainless steel reactors, liquid nitrogen cooling loop(-70°C to -80°C), ammonia recovery system, dual valve funnel for loading of the alkali metal, nitrogen or argon blanketing, **Acetylene/Ethylene Oxide**



Birch Reductions

Preparation of Lithium Acetylides



In-situ Sodium Amide as a Base for Elimination

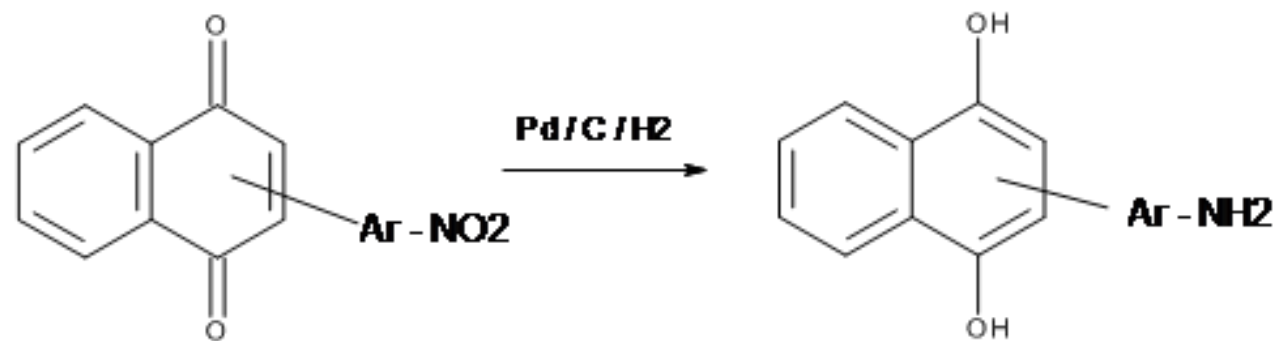
# Special Technologies

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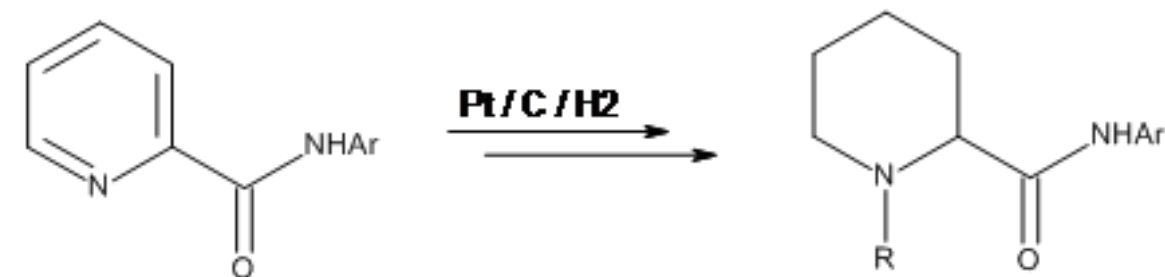
## Hazardous Reactor Systems - HIGHLIGHTS

### ➤ Catalytic Hydrogenations

- 1 x 2600 L stainless steel reactor, maximum pressure of 10 bar, possibility to utilize other gases like CO



Palladium Catalyzed Reduction of functional groups



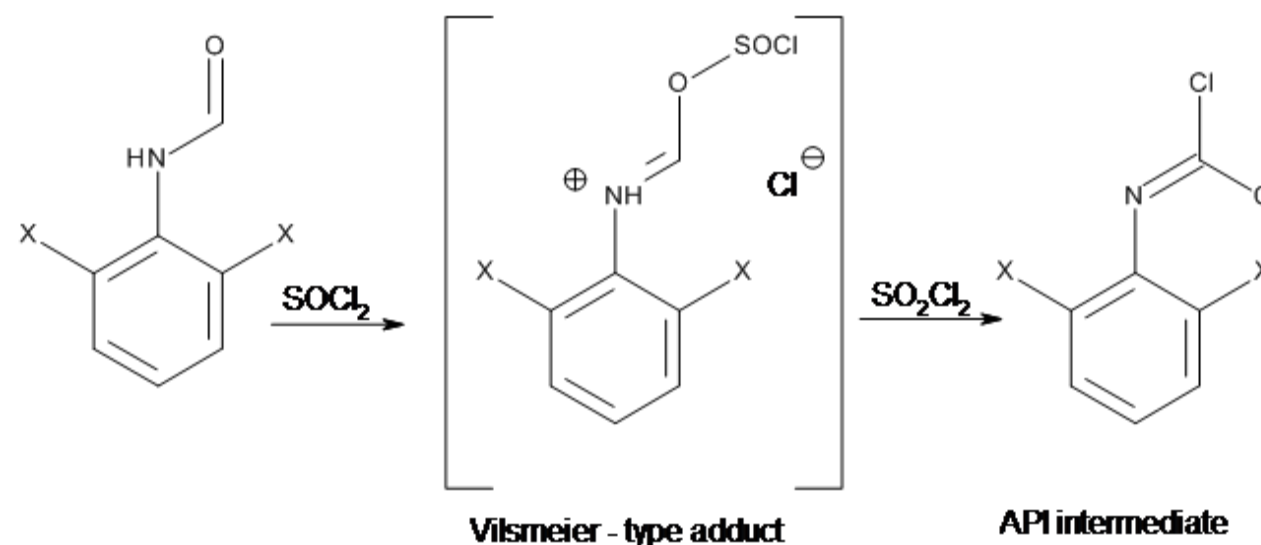
Platinum catalyzed Saturation of heteroaromatic Nuclei

# Special Technologies

## Hazardous Reactor Systems - HIGHLIGHTS

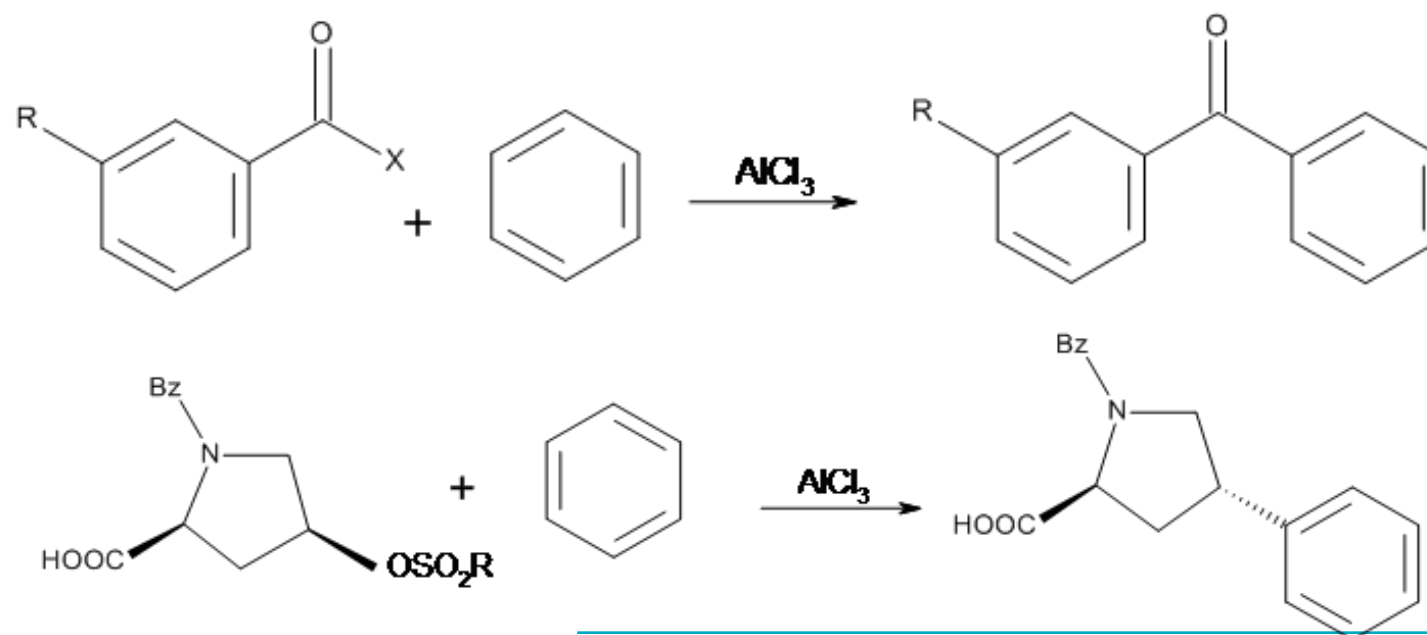
### ➤ Vilsmeier-type

- 1 x 3000l Glass-lined reactor



### ➤ Friedel-Crafts

- 1 x 2000l glass-lined reactor with Aluminum dosing system



# Special Technologies

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## Hazardous Reactor Systems - HIGHLIGHTS

### ➤ Cyanations

- 1 x 1600l glass-lined reactor (working volume range 300 L – 1300 L) with dedicated aqueous hypochlorite scrubber

### ➤ Oxidations: Hydrogen Peroxide – NaClO / TEMPO

- 800l Oxide prep tank, 4000l glass-lined reactor

### ➤ Mild Nitrations

- 1 x 1300 L glass lined reactor, collector lines for the emissions to avoid nitric oxides mixing with organic solvents



## Technologies Large Chemical Toolbox Including

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- **Acylations:** Schotten-Baumann, Friedel-Craft
- **Halogenations:** Bromine, Phospho-Chlorinated Derivatives, Thionyl Chloride
- **Distillation 20 TP, Thin layer evaporation**
  - Many reactors have distillation units for product and solvent purification
- **Reductions:** NaBH<sub>4</sub>, Birch
- **Handling of Grignard Reagents**

### Special Reagents

- DMSO<sub>4</sub>
- Benzene
- Carbon Monoxide Possible
- Gaseous Hydrogen Chloride
- N-, O- Alkylation
- Biomass Extraction

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**Our Strength: Wide Range of Chemical Processes under GMP**



# CDMO Project Management Flow



# Case Study I – GMP Advanced Intermediate

Transferred from non-GMP Asian Vendor

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Information from the customer

Pilot plant scale process, five step sequence with four purification steps:

1st step: preparation of the first RSM intermediate – Aldolic condensation  
Required two purifications: distillation on thin layer evaporator followed by rectification

2nd: step: Functional group protection (not isolated intermediate)

3rd step: Coupling reaction based on the utilization of a Grignard reagent (not isolated intermediate)

4th step: Functional group deprotection (not isolated intermediate)

5th step: Oxidation reaction with stoichiometric excess of oxidant and waste (crude final product)

Two purifications by crystallization to obtain the final product

Analytical methods for RMs or IPCs were not well defined

No safety data regarding

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# Case Study I – GMP Advanced Intermediate

Transferred from non-GMP Asian Vendor

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## Activities

Activity 1 - Preliminary assessment and proof of concept of the synthesis route on a laboratory scale, analytical method development

Activity 2 - Plant scale manufacturing of the first synthesis intermediate and characterization of its impurity profile as a key step for the feasibility

Activity 3 - Pilot plant scale trial of the final product to test process changes to overcome some difficulties observed during laboratory experimentation.

Activity 4

Plant scale production of three validation batches

# Case Study I – GMP Advanced Intermediate

Transferred from non-GMP Asian Vendor

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## Achievements

- ✓ Successful transfer of the distillation for the purification of the starting material (key technology)
  - ✓ Leaner overall process thanks to the improvement of reactions work-up
  - ✓ Development of a proper analysis method for the starting material
  - ✓ Increase of the yield of the last synthesis step following the substitution of the stoichiometric oxidant-based oxidation (excess reagent, low reproducibility, low yield, large amount of waste) with a more friendly catalytic system based on the utilization of a cheaper oxidant.
  - ✓ Improvement of the impurity profile of the final product.
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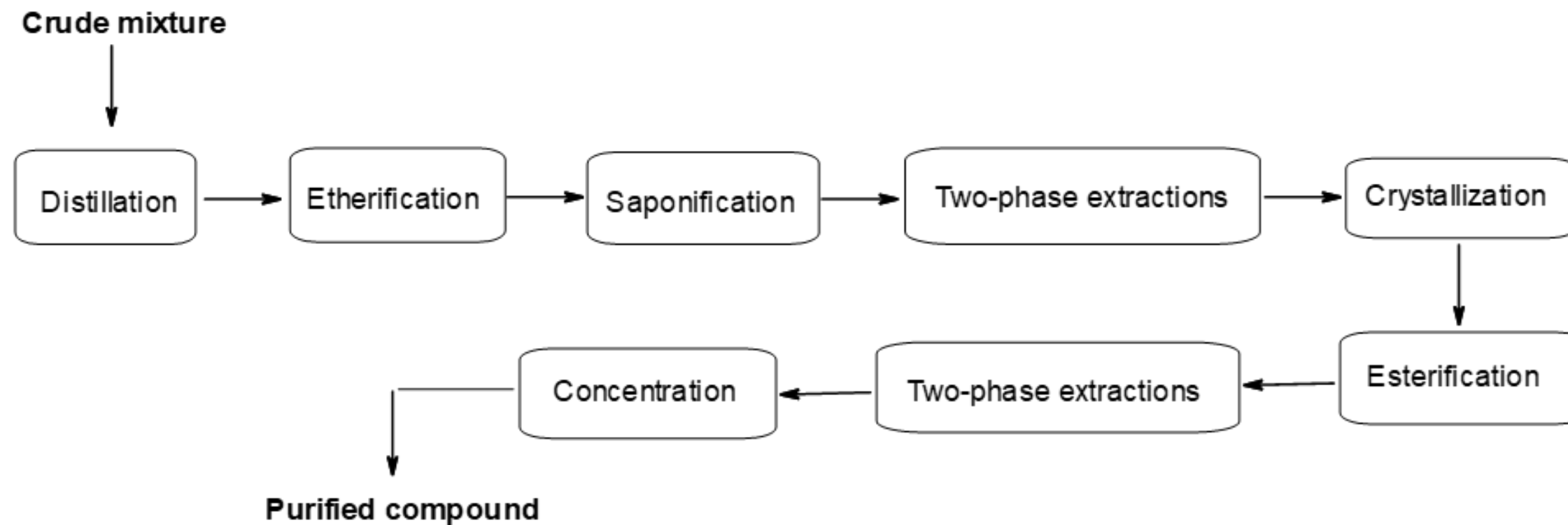
# Case Study II – GMP Advanced Intermediate

API intermediate to be recovered from a complex mixture of related by-products

No technical package available

## Description:

- Chemistry etherification, saponification, purification steps (distillation, precipitation, two-phase extraction)
- Process three reaction steps and several different purifications
- Block diagram of the process



# Case Study II – GMP Advanced Intermediate

API intermediate to be recovered from a complex mixture of related by-products

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## Activities and timing

- |                               |  |
|-------------------------------|--|
| <u>Laboratory activity</u>    | Identification of all the critical impurities of the material to be recovered and search for impurity-tailored treatments to obtain a proper quality product. Development of a general effectiveness purification process. |
| <u>Non GMP plant activity</u> | Scale-up of the laboratory method on the pilot plant   |
| <u>Plant activity</u>         | Plant scale manufacturing of three validation batches of the intermediate.   |

# Case Study II – GMP Advanced Intermediate

API intermediate to be recovered from a complex mixture of related by-products

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## Achievements

- Development of a recovery procedure of general effectiveness based on impurity-specific treatments.
- Characterization & definition of the main critical impurities of the material
- GMP manufacturing process for the recovery on a plant-scale
- Quality & Regulatory documentation to be put into customer's ASMF.

# Plants, Equipment & Utilities

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**Our strength, seasoned and highly experienced plant manager and operators handling Energetic Reactions and our toolbox Day-by-day.**



# Plants, Equipment & Utilities

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## UNIT 1:

### Pilot Plant / small manufacturing Plant

- 5 Glass lined reactors 300 – 800 L
- 6 SS reactors 150 – 1500 L
- 2 Centrifuges: Hastelloy (300L), Stainless Steel (300L)
- Distillation unit with 20 theoretical plates
- Vacuum Tray Dryer (20 – 50 kgs batch size)

### Utilities

-5° C - + 150°C

Reaction Pressure: 1 bar

Equipment Control PLC local

Deionized Water



# Plants, Equipment & Utilities

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## UNIT 2: Production

- 13 Glined reactors 800 - 4000 L
- 18 SS reactors 1000 – 6000 L
- 6 Centrifuges: Stainless Steel 300L- 600 L
- Dryer Pressure Filter 2000L
- Liquid/Liquid counter current extractor
- SS distillation column 500 L

### Utilities

-40° C to 150°C

Reaction Pressure to 6 bar

Centralized Solvent Distributor

Equipment Control PLC local

Deionized Water



# Plants, Equipment & Utilities

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## UNIT 3: Production

- 20 Glass lined reactors 1200 – 7000 L
- 16 SS reactors 1200 –12000 L
- 6 Centrifuges 300L- 600L
- 6 Pressure Filters 1300L - 2600L
- Distillation Unit up to 250°C
- Thin Film Evaporator
- 2 Filter dryers

### Utilities

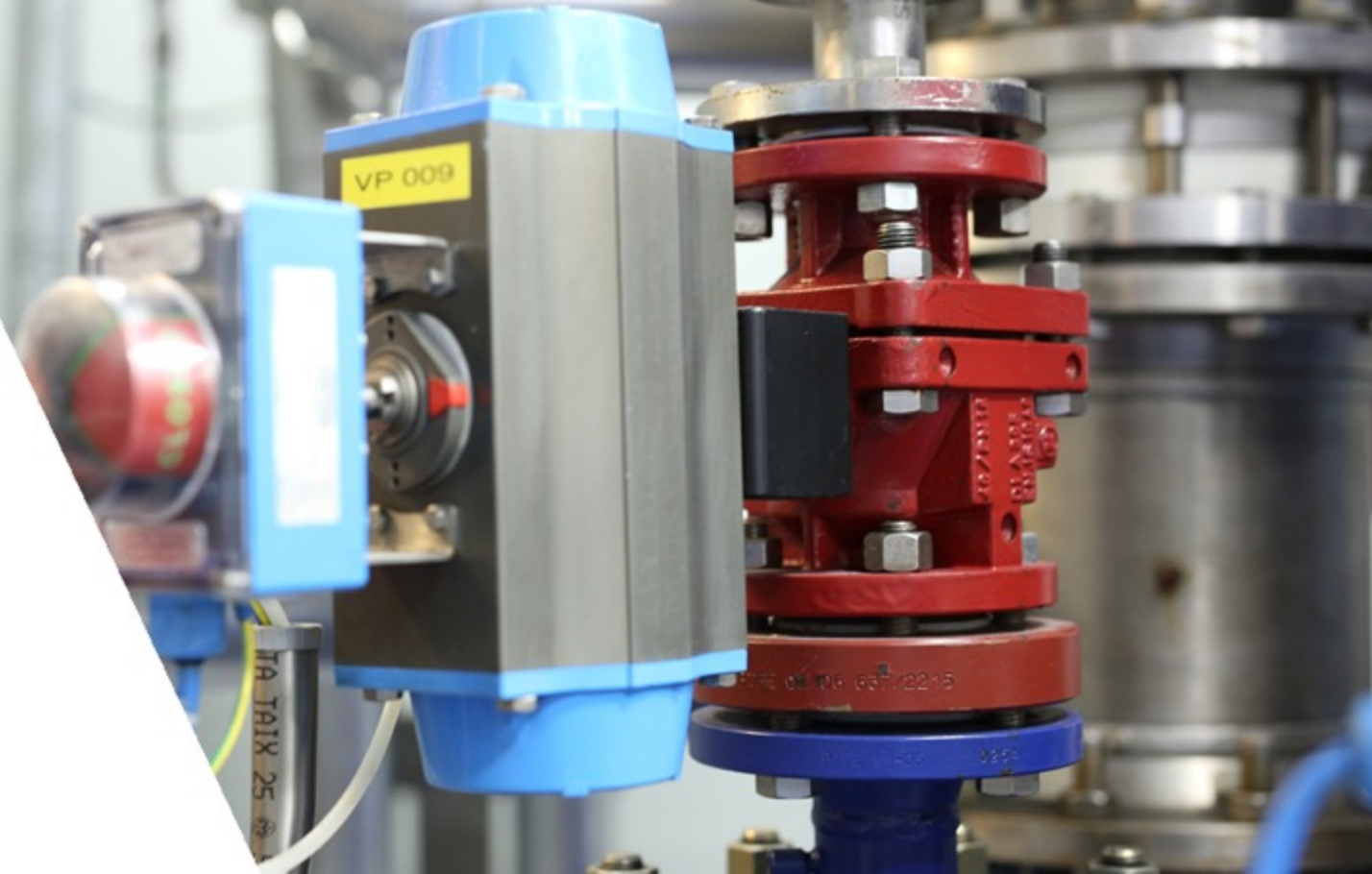
-5° C to 250°C

Reaction Pressure to 6 bar

Centralized Solvent Distributor

Equipment Control PLC local

Deionized Water



# Plants, Equipment & Utilities

## Unit 4: Production

- liquid NH<sub>3</sub> (-80°C), Hydrogenation (10 bar)
  - Cyanide, Sodium or Lithium,
  - Ethylene Oxide, Acetylene
- 
- 1 Glass Lined reactor 2000 L
  - 3 SS reactors 3000 L
  - 2 SS Autoclaves 1200L, 2400L
  - Centrifuge: Halar 600L
  - Centrifuge SS 300 L



## Utilities

-70-80° C to + 150°C

Reaction Pressure: -1 to 6 bar

Centralized Solvent Distributor

Equipment Control PLC local

Deionized Water

# Plants, Equipment & Utilities

## API Finishing Plant

Inox line

Glass lined, Teflon lined and anticorrosive steel line

Solvent recovery

Automated Warehouse

Purified Water

Equipment	Number	Volume
Glass lined vessels	2	6300 L
Stainless Steel vessels	2	6300 L
Hastelloy Centrifuge	1	1000 L
Horizontal SS Centrifuge	2	500 L, 1000 L
Turbodry Vaccum Dryer	2	3000 L
Distillation Column Stainless Steel for Rectification	1	6300 L
Distillation Column GL for Rectification	1	6300 L

# Plants, Equipment & Utilities

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## Drying Plant

- 2 Fluid bed dryers
- 4 Turbodry Vacuum Dryer 2000 L
- 1 Rotating Vacuum Dryer 500
- Class 100,000
- low bioburden for injectable API

## Utilities

20° C to 150°C

Reaction Pressure: 1 bar

Deionized Water



# Plants, Equipment & Utilities

## Solvent Handling

- Methylene Chloride
- 1,2 Dichloroethane
- Chloroform
- Pure Ethanol (non-denatured)
- Methanol
- Isopropanol
- Cyclohexane
- Acetone
- Xylene
- Toluene
- Benzene
- DMF
- Methyl Isobutyl Ketone

Solvent storage tanks : 3 – 30 m<sup>3</sup>

## Purified Water Loop

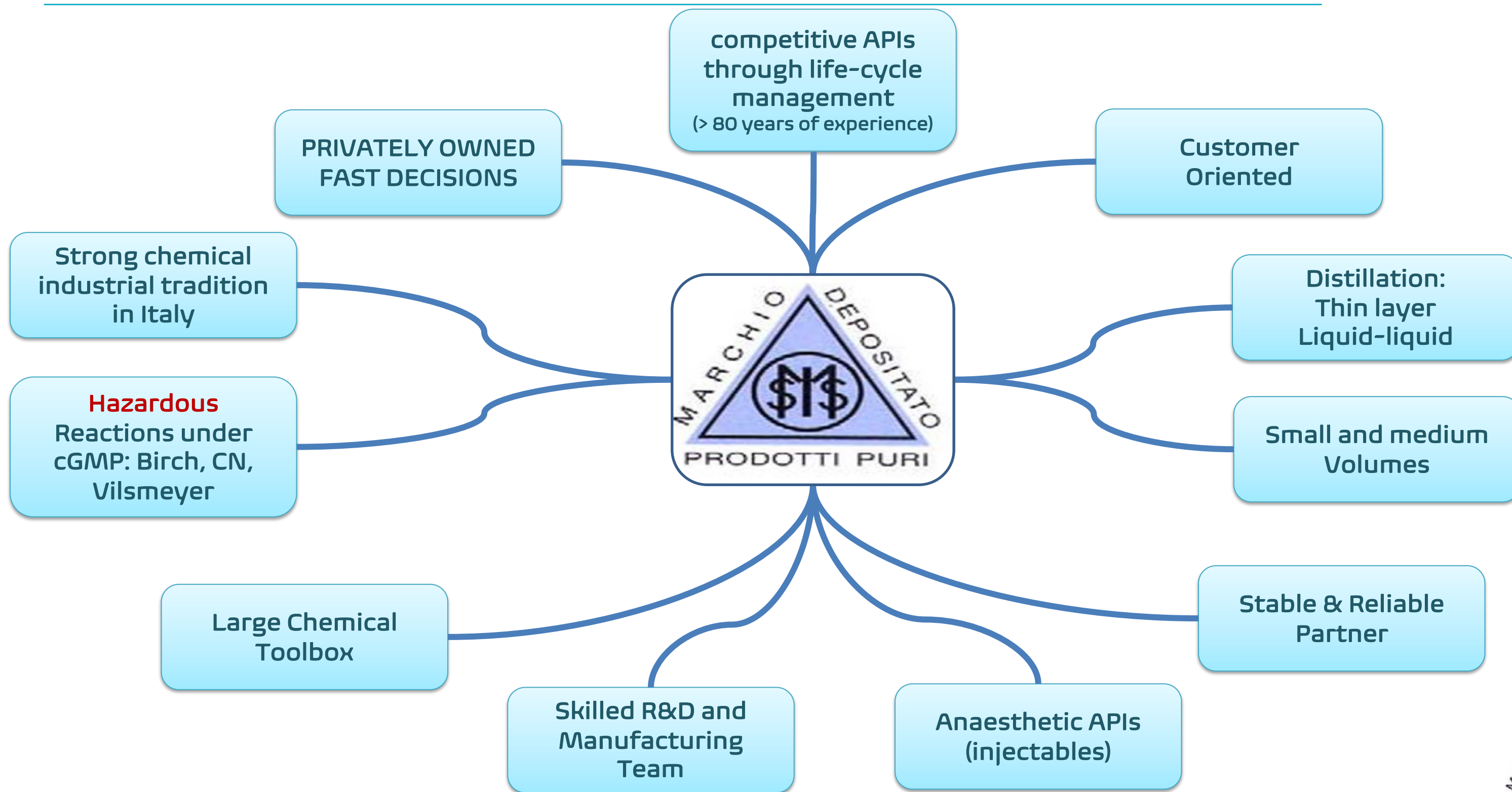
Capacity 3500 L / hour  
Conductivity (20°C) <1.1 µS/cm  
Bioburden <100 UFC/ml  
TOC < 500 ppb

## Demineralized Water

**Our Strength: Solvent Recovery**



# Why SIMS?





We are looking forward  
to a journey with you!

Contact Us

Riccardo Bulli

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Web: [www.simsitaly.it](http://www.simsitaly.it)



# ATTACHMENT 1: Commercial APIs

API	Therapeutic class	E-DMF	CEP	US DMF
Articain HCl	Dental anaesthetic	✓	✓	
Bupivacain HCL	Local anaesthetic	✓	✓	✓
Lidocain Base	Local anaesthetic	✓	✓	✓
Lidocain HCl	Local anaesthetic	✓	✓	✓
Mepivacaine HCl	Local anaesthetic	✓	✓	
Xibornol	Local infection and inflammation treatment	✓		
Ketoprofen	Anti arthritis	✓	✓	✓
Ketoprofen Lysine salt	Anti arthritis	✓		
Clonidine Base	Arterial hypertony	✓		✓
Clonidine HCl	Arterial hypertony	✓		✓
Dipyridamole	Antithrombotic		✓	✓
Ticlopidine HCl	Antithrombotic	✓	✓	
Disodium Clodronate tetrahydrate	Anti-osteoporotic	✓		
Gemfibrozil	Lipid lowerer	✓		✓
Metoprolol Tartrate	Blood pressure lowerer	✓	✓	✓
Propanolol HCl	Arterial hypertony	✓		✓
Tetrahydrozoline HCl	Ophthalmic	✓		✓