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.rangoni.it/sims - e-mail: sims@rangoni.it - C/C Postale 11536505 - C.C.I.A.A. Firenze 208960 - Iscr. Trib. Firenze N. 30623
OUR BANKERS: - BANCA TOSCANA - Figline Valdarno Branch - Account Nr. 7272.51 - BANCA NAZIONALE DEL LAVORO - Florence Head Office - Account Nr. 16362


SIMS
1937
cGMP
CDMO
Tuscany
Nitration
Florence
Highest Quality
Liquid NH3
Photovoltaic
Bromination
Grignard
87 years
CEP
AIFA
Milling
Chlorination
Crystallization
Articain
280m3
Sieving
Ketoprofen
Bromination
DMSO4
Friedel-Crafts
PMDA
COS
SIMS
Grignard
Tuscany
Family Business
European Source
-80°C
Italy
10 bar
US FDA
generic APIs
Hydrogenation
Schotten-Baumann
Energetic Chemistry
Local Anaesthetics
Chlorination
European Source
ANVISA
Lidocain
Liquid NH3
Birch
Hazardous Processes
Reggello
Photovoltaic
Lidocain
Two-Phase-Extraction
Ketoprofen Lysinate
Micronization
Halogenations
Passion for Chemistry
Next Generation
Vilsmeyer
Ketoprofen
Hazardous Processes
Bupivacain
Local Anaesthetics
Hydrogenation
APIs for injection
Energetic Chemistry
Class 100'000
generic APIs
N-,O-Alkylation
Highest Quality
Halogenations
cGMP
Articain
High Temp Distillation

SIMS

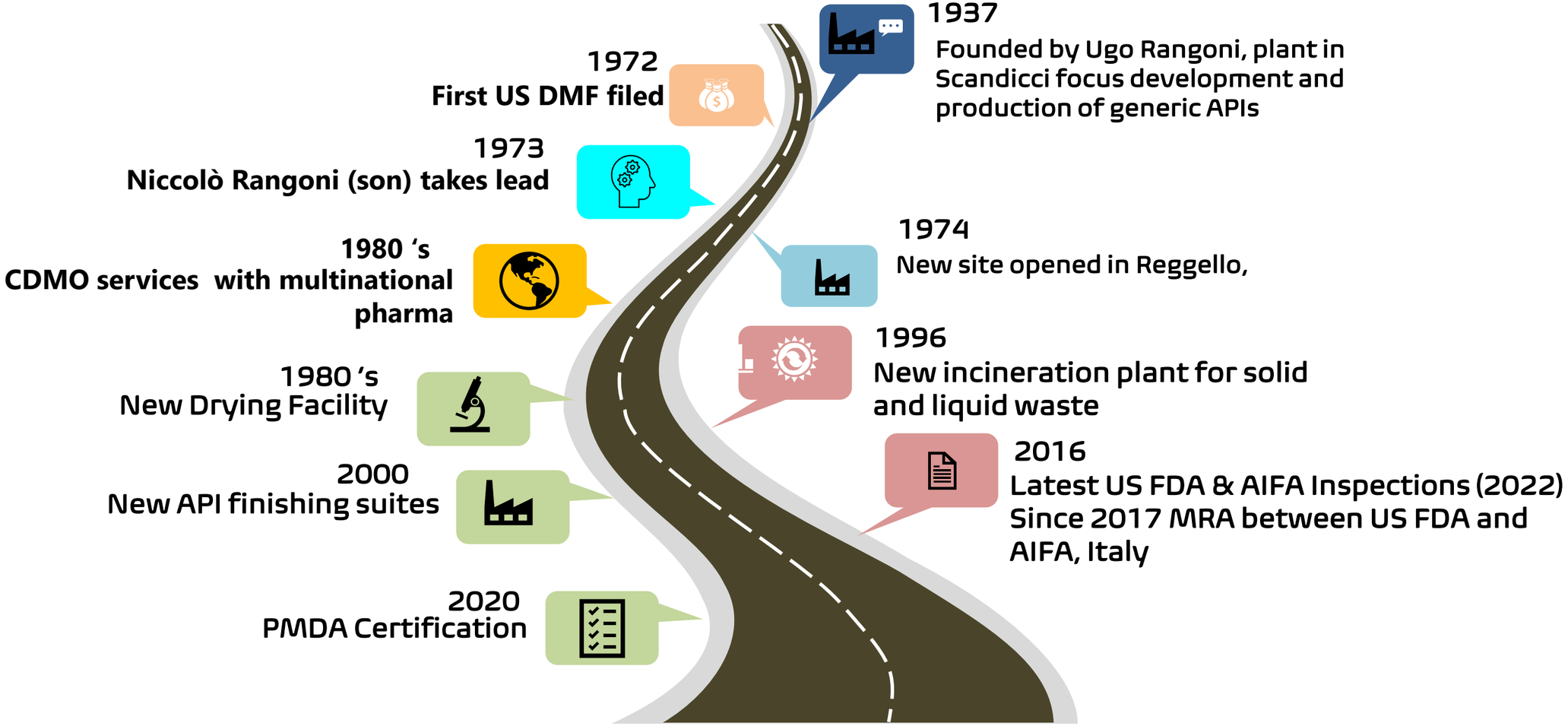
Our CDMO Services

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.

MARCHIO DEPOSITATO
PRODOTTI PURI

History

S.I.M.S. where Technology meets Tradition



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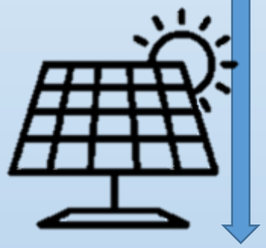
PRODOTTI PURI

SIMS INVESTMENTS OVERVIEW

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

2021 **2022** **2023** **2024** **2025**





300K€ **215K€** **800K€** **1.2M€** **1.5M€**

INVESTMENTS on specific plants
such as the incineration plant &
the purification plant

INVESTMENTS on energy systems
revamping of some energy-intensive plants, with the aim of reducing energy costs

GREATER INVESTMENTS to gain energy efficiency, renew R&D laboratories and improve other departments & productive units
preparation and construction of photovoltaic plant(30% of energy use), renewal of R&D labs, reduction of waste costs and software adaptation to GMP data integrity requests for plant

1 year

1 year

3 years horizon

New Photovoltaic Plant on SIMS' Roofs 2024 on stream

INTRODUCTION

At a glance

- Corporate Info
- History
- Certifications
- Technology & Strengths
- PR&D
- Production plants
- EHS

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

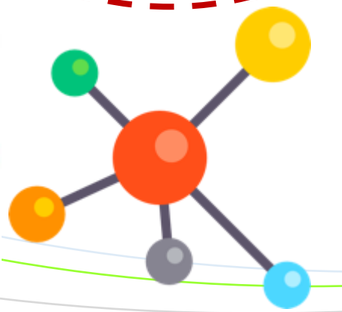
Real Estate

MINIERE DI FIZZANO

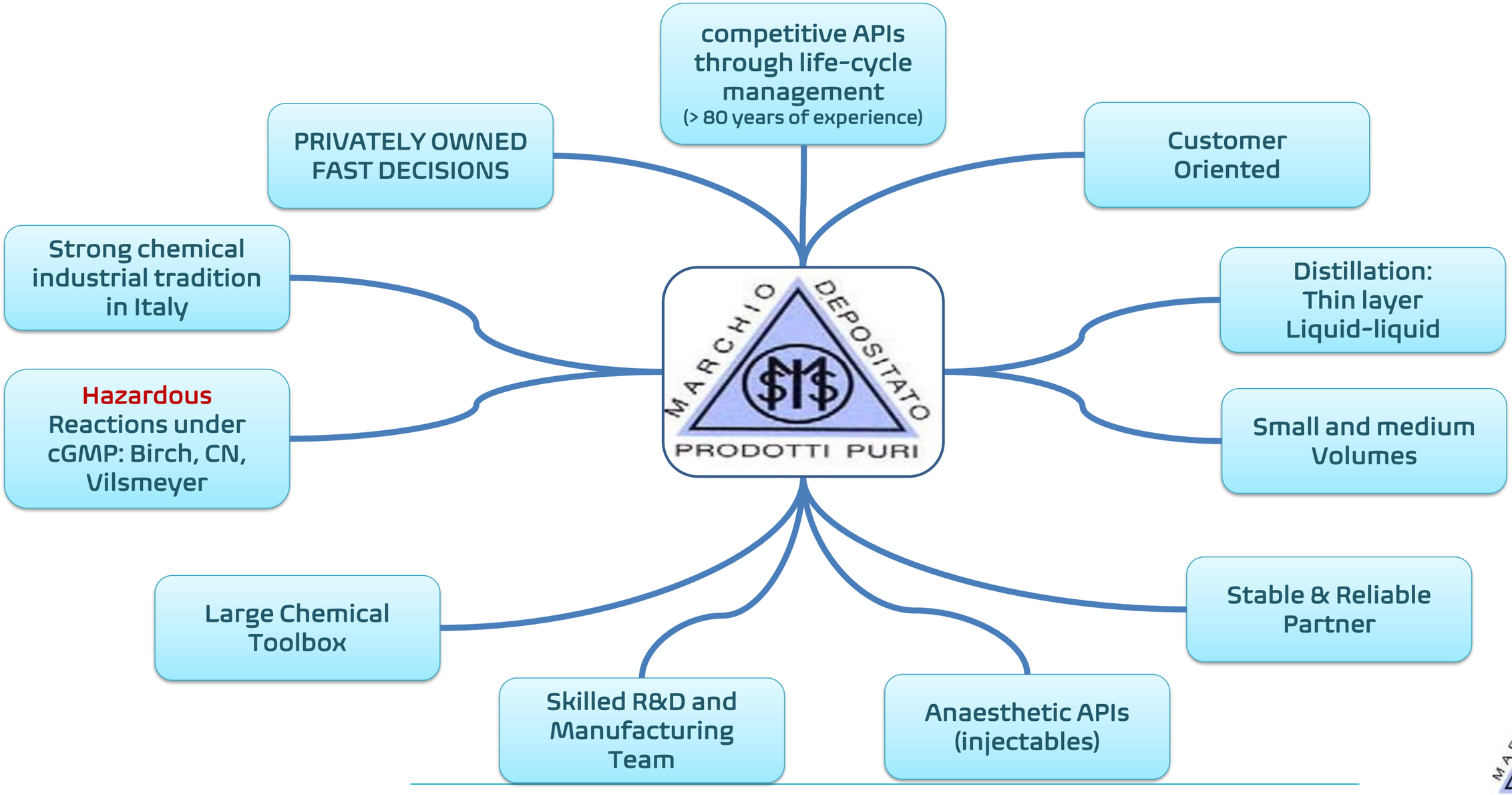
Beach Club

AZIENDA AGRICOLA LE FALLE

Wine & Oil Production



Why SIMS?


competitive APIs through life-cycle management
(> 80 years of experience)
PRIVATELY OWNED FAST DECISIONS
Customer Oriented
Strong chemical industrial tradition in Italy
Distillation: Thin layer Liquid-liquid
Hazardous Reactions under cGMP: Birch, CN, Vilsmeyer
Small and medium Volumes
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PRODOTTI PURI
Large Chemical Toolbox
Stable & Reliable Partner
Skilled R&D and Manufacturing Team
Anaesthetic APIs (injectables)

LOCATION

Located 30 km South East of Florence, Italy

Opened in 1974, operation was moved from the original site

<u>By train:</u>

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

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

<u>By car:</u>
30 min from the airport
25 min from central Florence

<u>By flight:</u>
From any main airport in Europe to Florence Airport

SOME FIGURES

Sales 2021: € 11.8 Mio
Sales 2022: € 12.7 Mio
Sales 2023: € 16.2 Mio

- Generic API's: 75%
- CDMO: 25 %

By Geography:
- Europe: 62%
- America: 9%
- ROW: 29%

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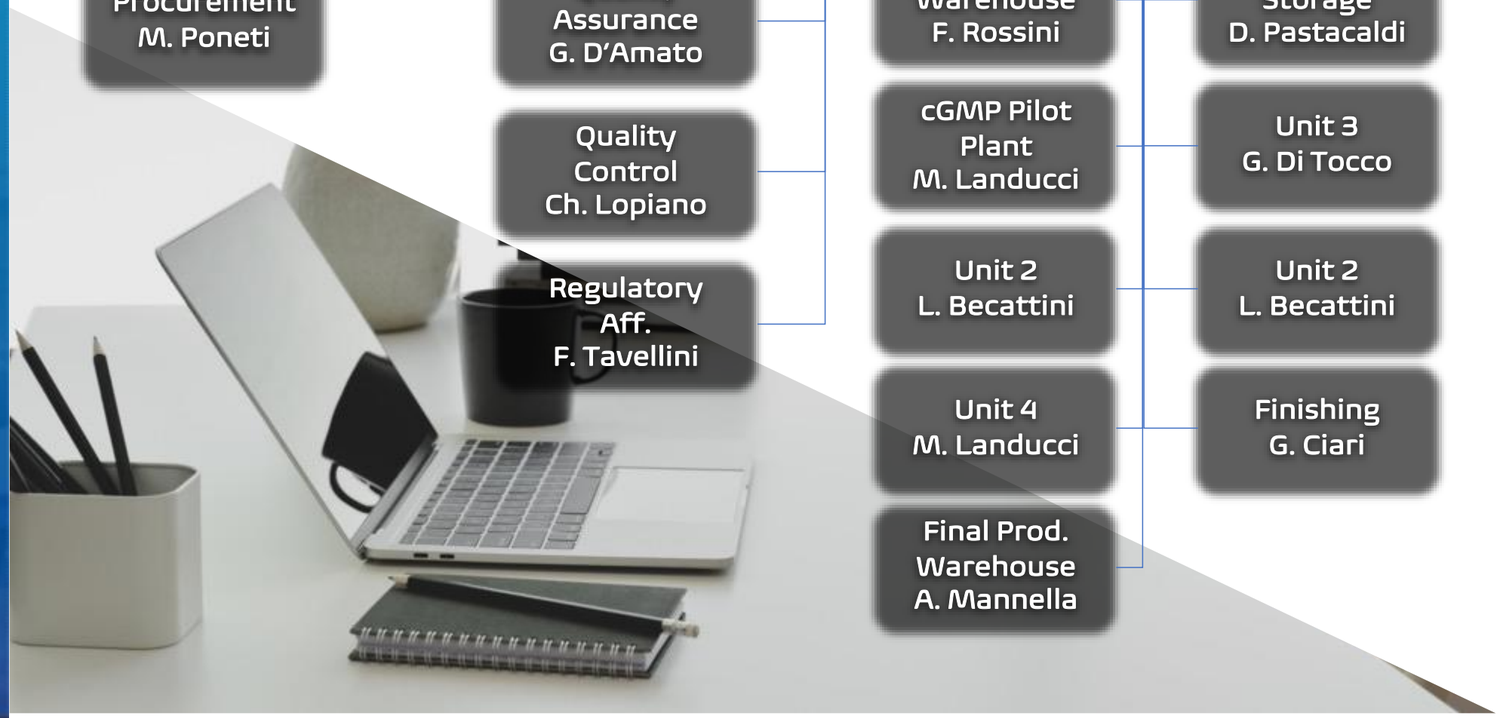
PRODOTTI PURI

ORG CHART

- President — N. Rangoni
  - Prevention & Protection — R. Ottato
  - General Manager — D. Frija
    - Administration — G. Pasquini
      - Procurement — M. Poneti
    - Mkt & Sales — R. Bulli
    - Quality Unit — F. Tavellini
      - Quality Assurance — G. D'Amato
      - Quality Control — Ch. Lopiano
      - Regulatory Aff. — F. Tavellini
    - Production — G. Di Tocco
      - RM Warehouse — F. Rossini
      - cGMP Pilot Plant — M. Landucci
      - Unit 2 — L. Becattini
      - Unit 4 — M. Landucci
      - Final Prod. Warehouse — A. Mannella
      - Solvent Storage — D. Pastacaldi
      - Unit 3 — G. Di Tocco
      - Unit 2 — L. Becattini
      - Finishing — G. Ciari
    - Technology — N. Celiberto
      - Maintenance — L. Lumini
      - IT — A. Bonaluti
    - R&D — M. Pisani Focati
      - Dev. Pilot Plant — M. Landucci
    - HSE — R. Ottato
      - Sewage Plant — F. Bartoli
      - Termocomb. — M. Iavarazzo



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PRODOTTI PURI

PEOPLE

105 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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INSPECTIONS & CERTIFICATES LIST

- Compliance with international cGMP
- With US FDA Inspections since 1970'

- AIFA March 2022
- 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

Our Strength:
Extensive Regulatory History
and Injectable API & Anesthetics

- **Since 2017 Mutual Recognition Agreement between US FDA and AIFA, Italy**

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CDMO Project Management Flow

Review	RFP Proposal	Process Evaluation Route Scouting	Initial propsal 2-4 weeks
SOW	Scoping	Detail Project plan	Project Order Agreement 2-4 weeks
Stage 1	Kick-off Lab trials	Full site review Process Confirmation & Familarization	R&D Report Update COG
Stage 2	Scale-up	Pilot Production DOE	Initial batches PD Reprot Update COG
Stage 4	Validation	Registration/Validation Batches	Product Delivery Validation Reports Final COG
Stage 5	Production Initiation	Regular Commerical Manufacturing	Product Supply

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Strengths

- Route Scouting - Our experience from generic API development serves to optimize COGS for Exclusive Products and support API Life Cycle Management;
- Raw Material evaluation – Cost and Risk Analysis;
- "Supply Chain Safety Assessment" (SCSA)
- Hazardous Reactions or Energetic Chemistry
- Continuous Improvement
- 280 m^3 of Total Reactor Capacity in 3 plants

Our Strength: Hazardous Processes under GMP

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

UNIVERSITÀ DI PISA

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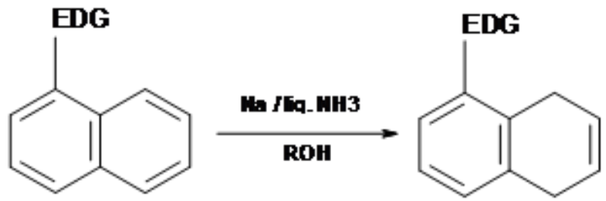
Special Technologies

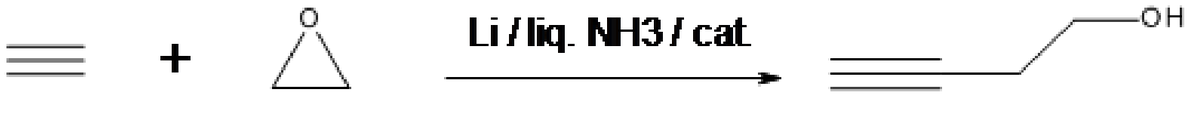
Hazardous Reactor Systems - HIGHLIGHTS

➢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



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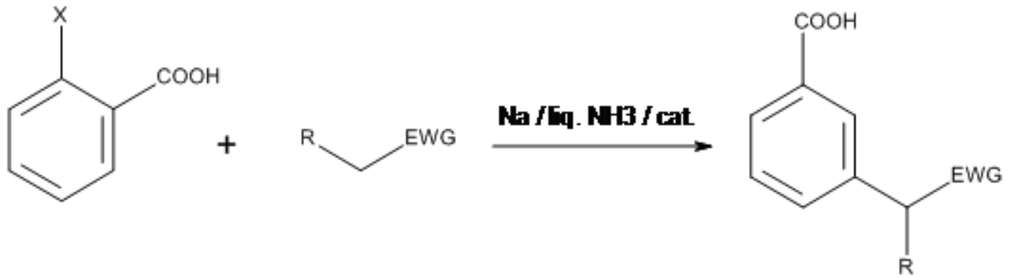
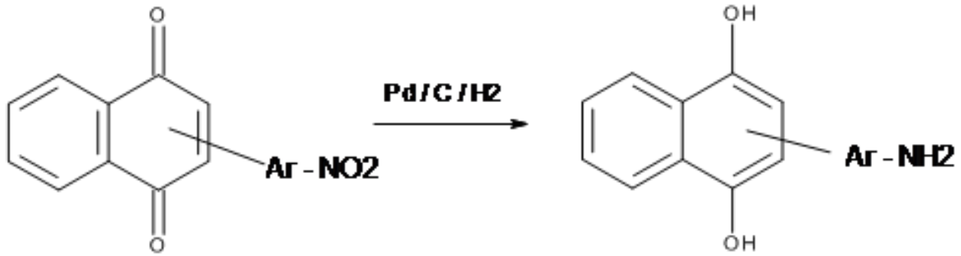


In-situ Sodium Amide as a Base for Elimination

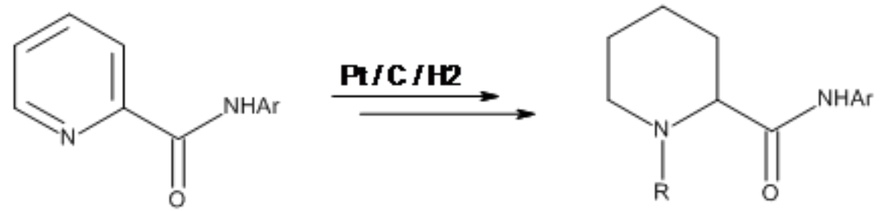
Special Technologies

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

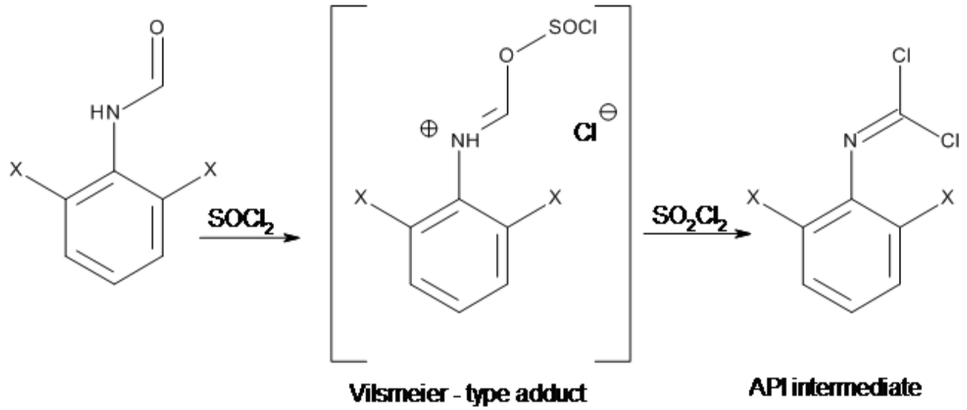


Platinum catalyzed Saturation of heteroaromatic Nuclei

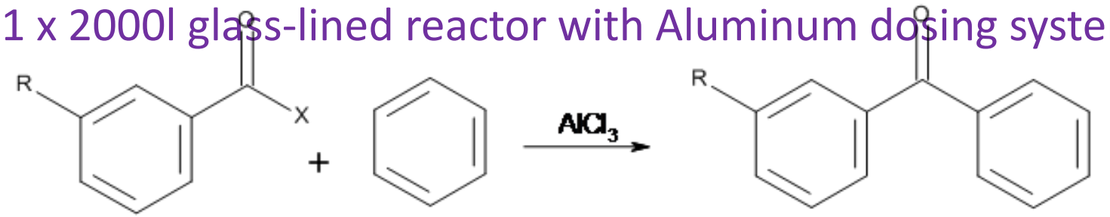
Special Technologies

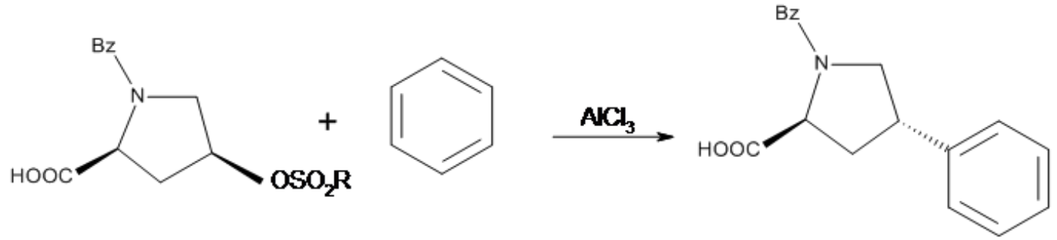
Hazardous Reactor Systems - HIGHLIGHTS

- **Vilsmeier-type**
  - 1 x 3000l Glass-lined reactor



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





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Special Technologies

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

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Technologies Large Chemical Toolbox Including

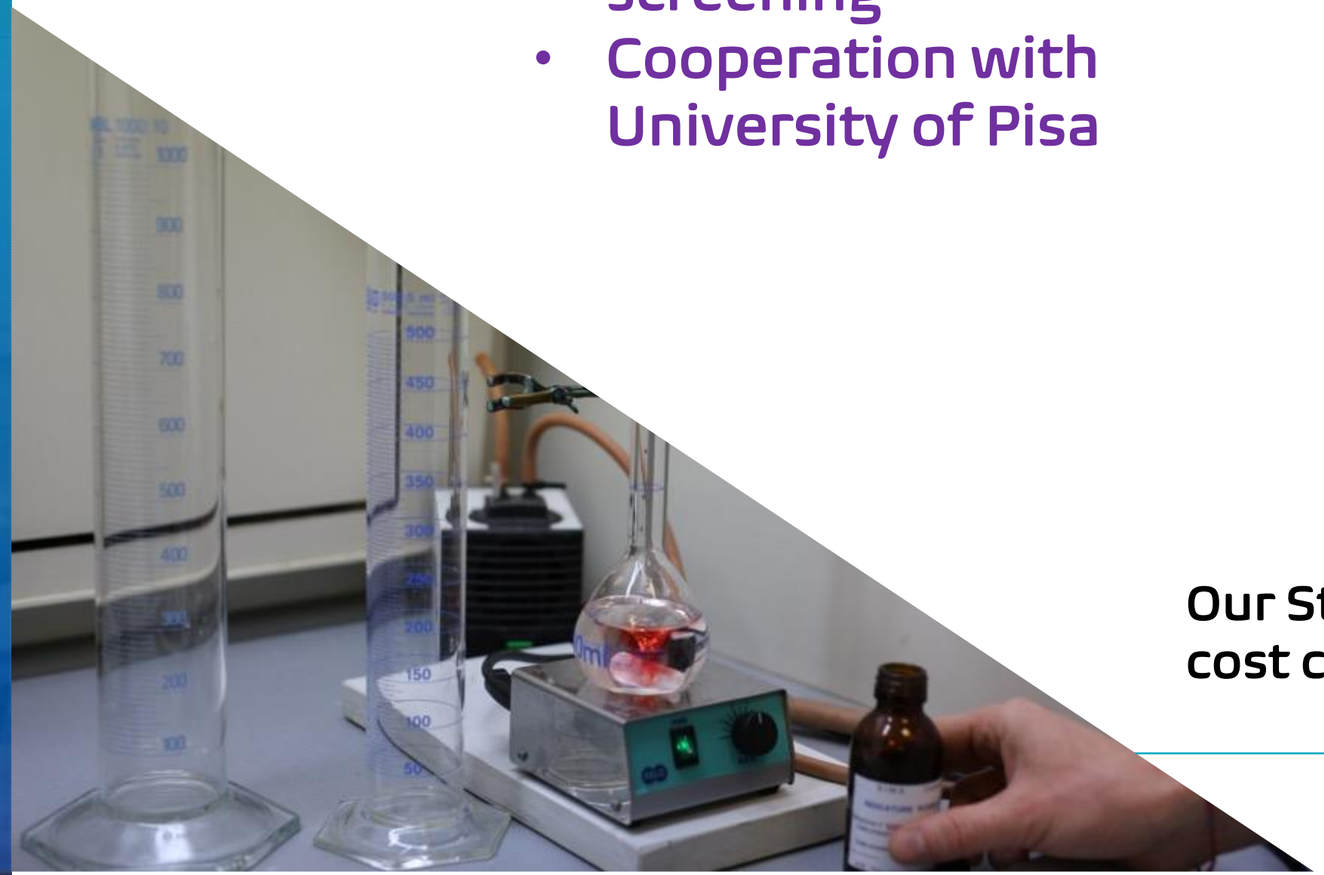
- **Acylations:** Schotten-Baumann, Friedel-Craft
- **Halogenations: Bromine**, Phospho-Chlorinated Derivatives, Thionyl Chloride
- **Distillation 20 TP, Thin layer evaporation**
  - Many reactors have distillation units for product and solvent purification
- **Reductions: $NaBH_4$, Birch**
- **Handling of Grignard Reagents**

Special Reagents

- $DMSO_4$
- Benzene
- Carbon Monoxide Possible
- Gaseous Hydrogen Chloride
- N-, O- Alkylation
- Biomass Extraction

Our Strength: Wide Range of Chemical Processes under GMP

R&D: Synthesis and Analytical Development



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

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Plants, Equipment & Utilities

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

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Plants, Equipment & Utilities

UNIT 1:

Pilot Plant / small manufacturing Plant

- GL reactors 300 – 800 L
- SS reactors 150 – 1500 L
- 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

UNIT 2: Production

- Glass lined reactors 800 - 4000 L
- Stainless Steel reactors 1000 – 6000 L
- Centrifuges: Stainless Steel (300L, 600L)
- Vacuum Pressure Filter 2000L
- Liquid/Liquid counter current extractor

Utilities
-40° C to 150°C
Reaction Pressure to 6 bar
Centralized Solvent Distributor
Equipment Control PLC local
Deionized Water

Plants, Equipment & Utilities

UNIT 3: Production

- Glass lined reactors 1200 – 7600 L
- Stainless Steel reactors 400 – 7000 L
- Centrifuges: Stainless Steel (300L, 600L)
- Vacuum Pressure Filters 1300L, 2600L
- Distillation Unit upto 250°C
- Thin Film Evaporator

Utilities

-5° C to 250°C
Reaction Pressure to 6 bar
Centralized Solvent Distributor
Equipment Control PLC local
Deionized Water

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Plants, Equipment & Utilities

Unit 4: Production

- liquid NH_3 (-80°C), Hydrogenation (10 bar)
- Cyanide, Sodium or metallic,
- Ethylene Oxide, Acetylene

- Glass Lined reactor 2000 L
- Stainless Steel reactor 4000 L
- Centrifuge: Halar (600L)
- Centrifuge Stainless Steel (300 L)

Utilities

-70-80° C to + 150°C
Reaction Pressure: -1 to 6 bar
Centralized Solvent Distributor
Equipment Control PLC local
Deionized Water

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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 Stainless Steel 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

Drying Plant

- 2 Turbodry Vacuum Dryer 2000 L
- 2 Rotating Vacuum Dryer 500
- Class 100,000
- low bioburden for injectable API

Utilities

20° C to 150°C

Reaction Pressure: 1 bar

Deionized Water

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Plants, Equipment & Utilities

Solvent Handling

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

Solvent storage tanks : 3 – 30 m^3

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

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Quality Control

- 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

Environment Health & Safety

- ✓ **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

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PRODOTTI PURI

We are looking forward to a journey with you!

Contact Us

Riccardo Bulli

Phone: +39 055 863051

Email: ***sims@simsitaly.it***

Web: www.simsitaly.it

Joseph Tessier – BD Consulting

Phone +420 603 528790

BACKUP SLIDES – MORE DETAILS

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	✓		✓

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Special Technologies

Hazardous Reactor Systems - HIGHLIGHTS

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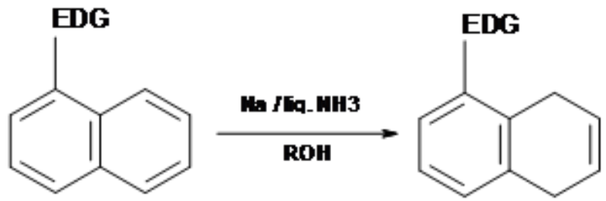

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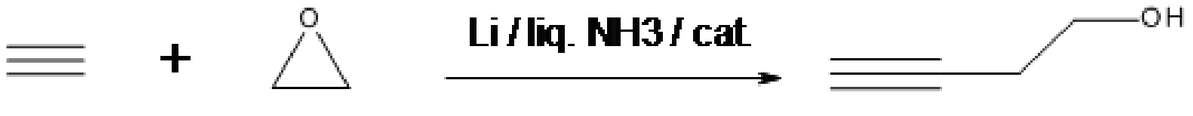

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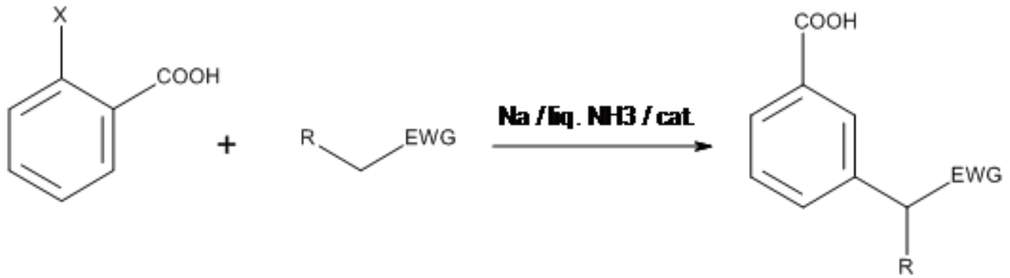

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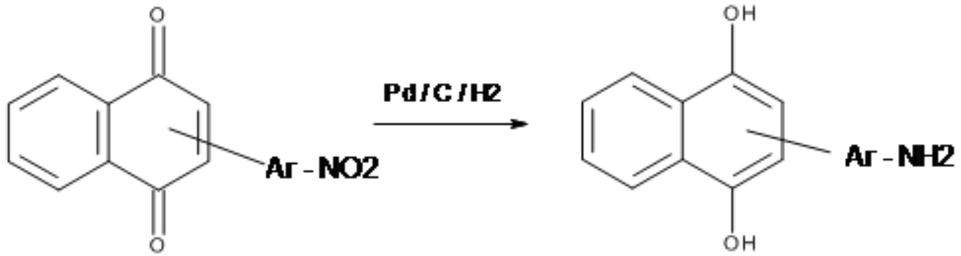

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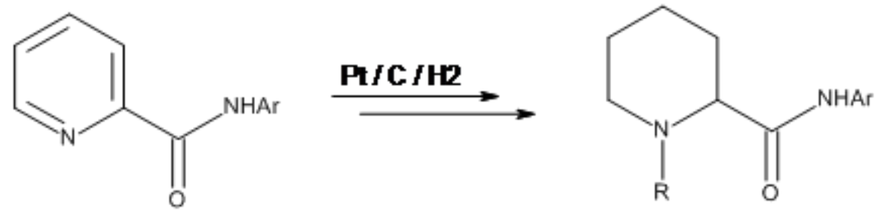

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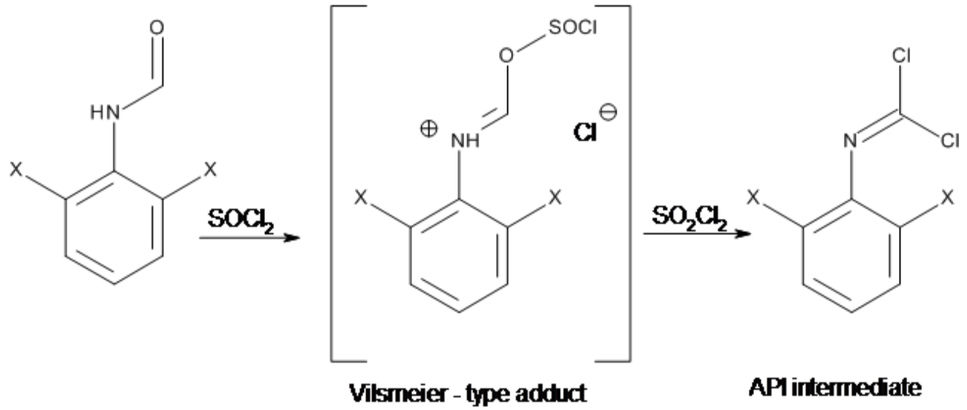

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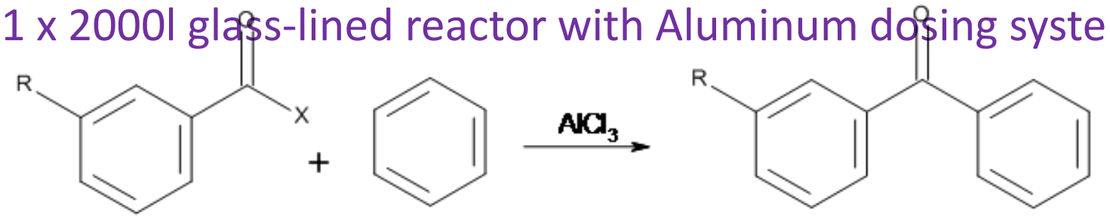
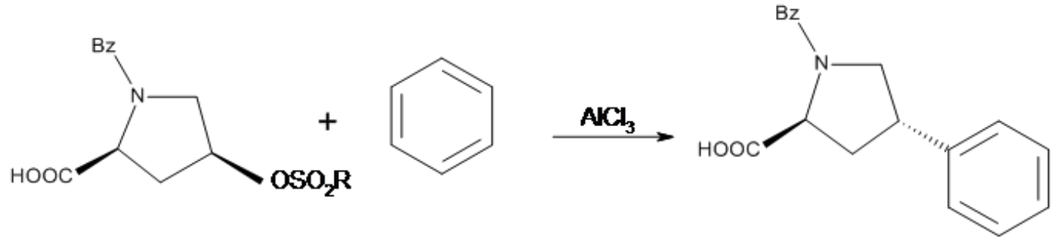
  - 1 x 2000l glass-lined reactor with Aluminum dosing system





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Case Study I – GMP Advanced Intermediate

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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

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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

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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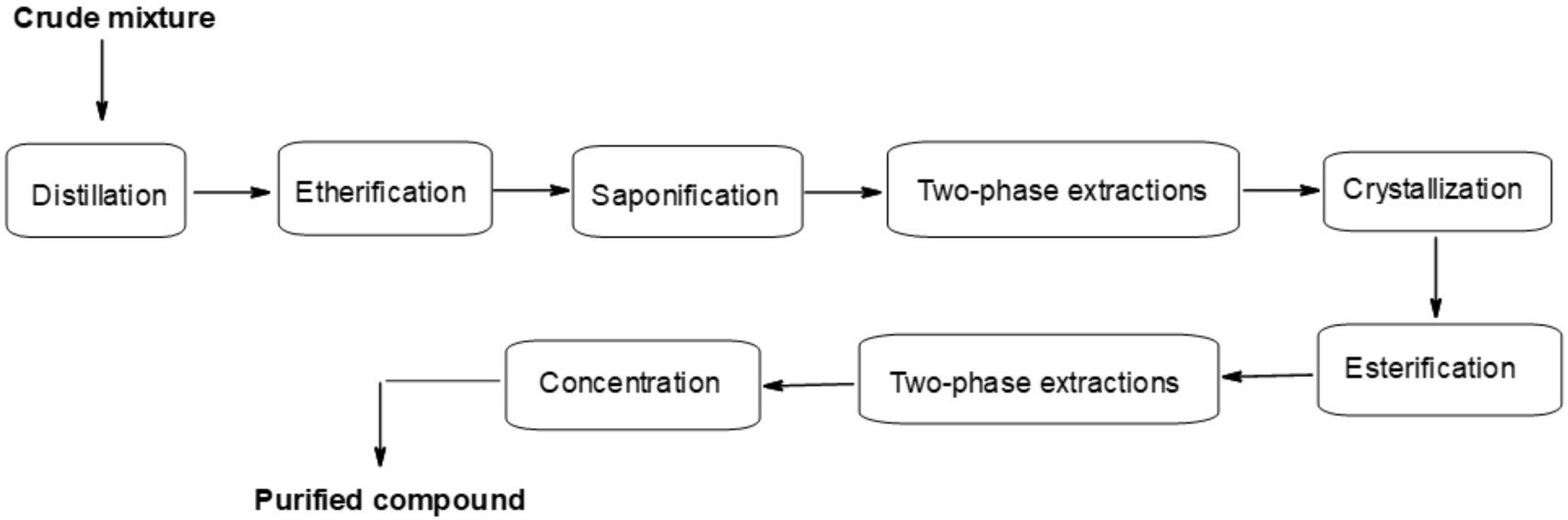
Case Study II – GMP Advanced Intermediate

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

Activities and timing

Laboratory activity	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.
Non GMP plant activity	Scale-up of the laboratory method on the pilot plant
Plant activity	Plant scale manufacturing of three validation batches of the intermediate.

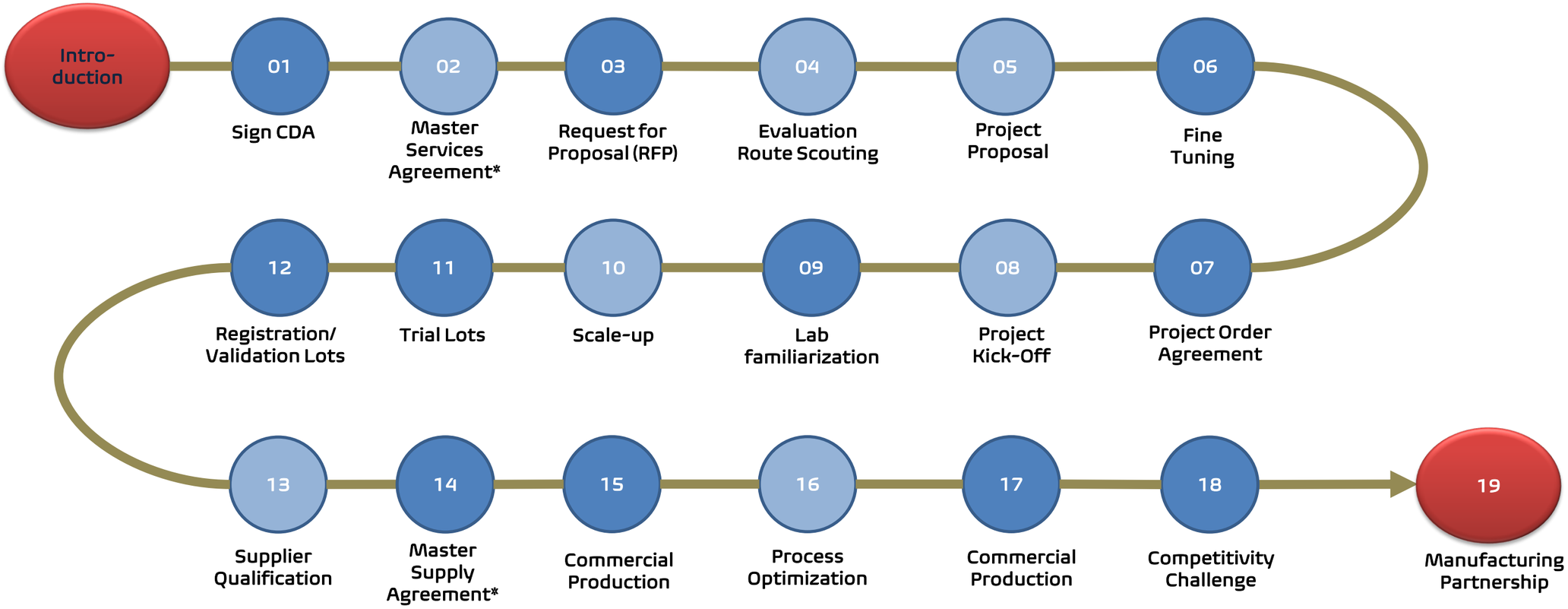
Case Study II – GMP Advanced Intermediate

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

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.

ATTACHMENT 1: CDMO Business Process



*) Master Services Agreements and Master Supply Agreements may be optional, while they are more and more requested by our clients.