

PolyCrystalLine

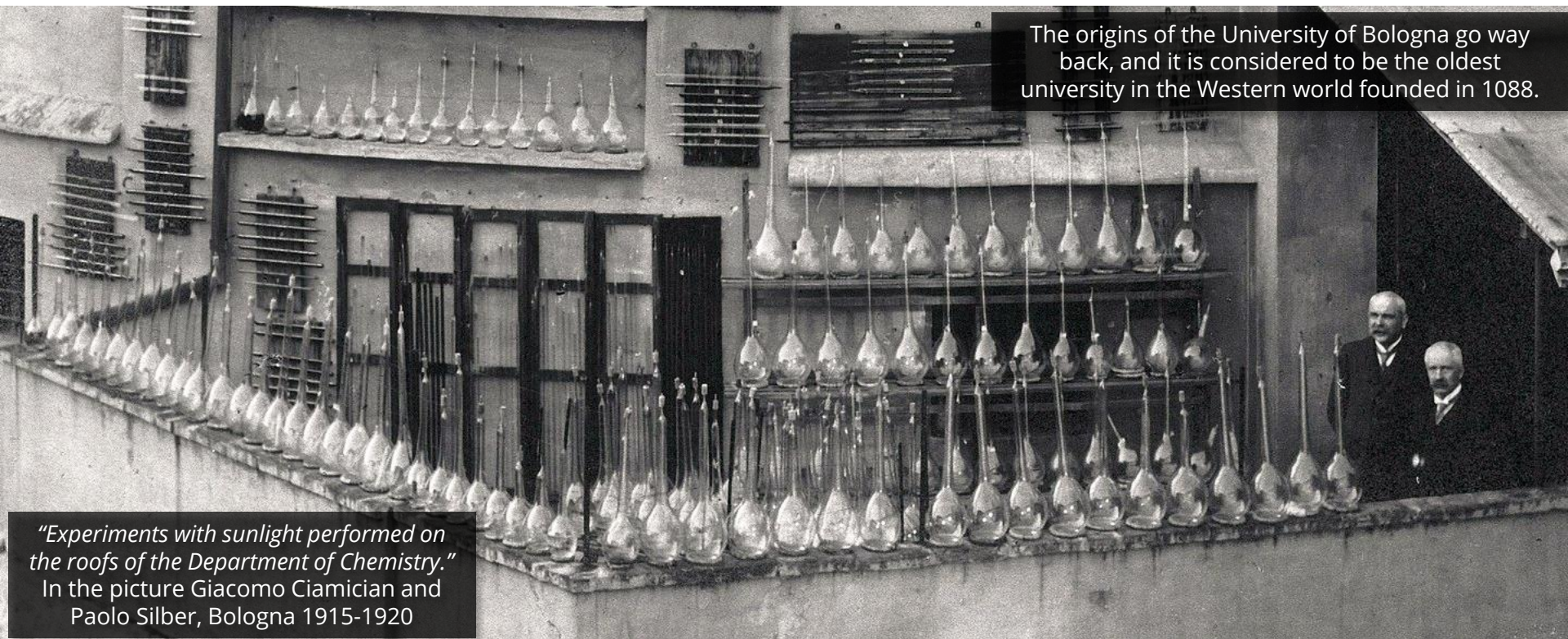
YOUR INTEGRATED SOLUTION PARTNER



**Excellence in Solid-State**

# WHERE WE STARTED

We began as a **start-up business** from the **University of Bologna**, the capital and largest city of the **Emilia-Romagna Region** in **Northern Italy**.



The origins of the University of Bologna go way back, and it is considered to be the oldest university in the Western world founded in 1088.

*"Experiments with sunlight performed on the roofs of the Department of Chemistry."*  
In the picture Giacomo Ciamician and Paolo Silber, Bologna 1915-1920

# WHY WE STARTED

In **2005** PolyCrystalLine was **self-founded** by a group of **young scientists** from the **Molecular Crystal Engineering Group of UNIBO**.

This was in response to the increasing interest from the pharmaceutical industry of a **hi-tech partner** specialized in **solid-state chemistry** able to **design** and **control** the **properties of API and drug products**.


*"The first research activities were carried out in a small laboratory, less than 1,000-square-foot, with limited equipment and capabilities."*

In the picture: Elena Dichiarante,  
Bologna 2006




# FROM START-UP TO COMPANY

In **2009** we moved our premises into **larger custom-built laboratories, 4,400-square-foot**, in **Medicina** an Italian *comune* in Bologna.

A photograph of a laboratory setup inside a fume hood. The setup includes a round-bottom flask on a magnetic stirrer, connected to a vertical glass column and other glassware by various tubes and clamps. The equipment is mounted on a metal frame. In the background, there are more laboratory benches and equipment.

"Setting up a chemical synthesis in a walk in fume hoods."  
Medicina 2009

A photograph showing a long, modern laboratory bench with white countertops and bright orange storage cabinets underneath. The room is well-lit with overhead fluorescent lights. In the background, there are more laboratory equipment, a doorway, and a storage area.

"R&D Department during its completion."  
Medicina 2009

# GROWTH WITH INNOVATION

We **constantly** invested in **capacity, technology, and people** who have a **passion** for developing solutions for clients with **complex challenges**.



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**Know-How and  
Tech Expertise**

# SOLID-STATE CHEMISTRY OF SMALL MOLECULES

Every instance of multiple crystal forms is **new** and **unique** and we have to fully **investigate**, **characterize** and **control** all forms.

**IT IS NOT POSSIBLE TO PREDICT:**



**HOW MANY**  
different crystal forms  
can be prepared

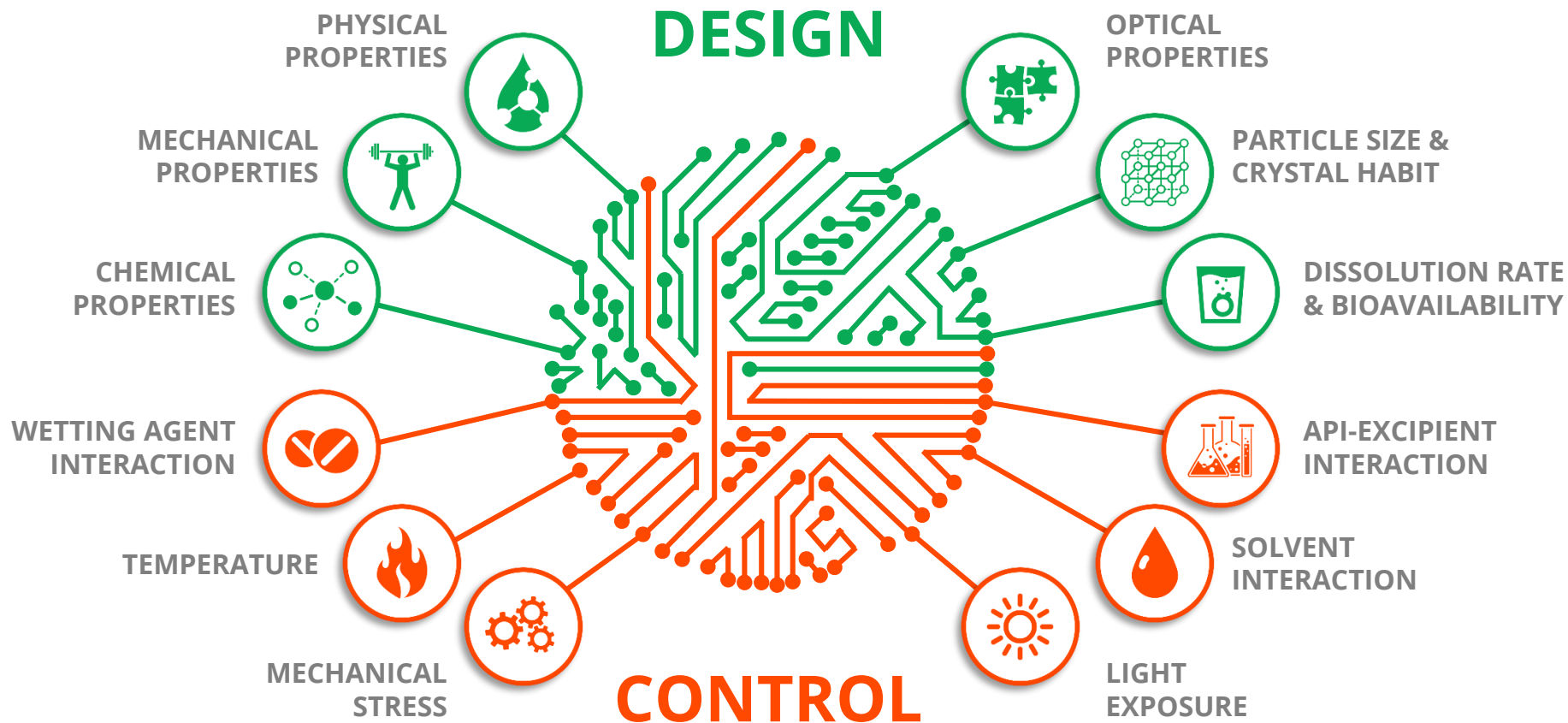


**HOW TO PREPARE**  
any, as yet unknown,  
crystal forms



**THE PROPERTIES**  
of any, as yet unknown,  
crystal forms

# WE DEVELOP HI-TECH API AND DRUG PRODUCTS



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# Services and Capabilities

# Discover

## Solid Form Screening



POLYMORPH  
SCREENING



CO-CRYSTALS  
SCREENING



SALTS  
SCREENING



SOLVATES /  
HYDRATES  
IDENTIFICATION



AMORPHOUS  
DISPERSION

# Solid Form Screening

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**AIM:** Screening of form of target API and investigation of crystallization systems to obtain them.

up to 9 weeks

We **DESIGN** our screen based on **TIME** and **MATERIAL AVAILABLE** offering a variety of screen types, which we **TAILOR** to your specific needs:

## Polymorph Screening



### STRATEGY:

Map a large amount of polymorphic space around the target API, thus identifying the most stable form.

## Amorphous Dispersion



### STRATEGY:

Investigate the formation of suited forms of target API combined with counterions, co-formers, and polymers.

## Co-Crystal Screening



## Salt Screening



**At least 20mg of material would be available for shipping to the client.**

# Discover

## Solid Form Selection



SOLUBILITY  
ENHANCEMENT



DRUG-EXCIPIENT  
COMPATIBILITY



STABILITY STUDIES



POWDER  
PROPERTIES

# Solid Form Selection

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**AIM: Identify and understand the most suitable form to move forward into development**

up to 2 weeks



## Target Form

- Solubility
- Physical and Chemical Stability
- Hygroscopicity
- Handling, Flow and Manufacturability



## Powder Properties

- Purity and Yield
- Impurity Levels
- Morphology
- Particle Size



## Stability Studies



## Comparative Dissolution



## Excipient Compatibility

**At least 250mg of material would be available for shipping to the client.**

# Analyze



THERMAL  
ANALYSIS



PHYSICO  
CHEMICAL  
PROPERTIES



STRUCTURAL  
CHARACTERIZATION



WATER  
CONTENT



METHOD  
DEVELOPMENT  
& VALIDATION



cGMP  
QUALITY  
CONTROL



RHEOLOGICAL  
PROPERTIES



## Structural Characterization

### X-RAY DIFFRACTION

- **Powder Diffraction** (PANalytical X'Pert3 Powder) *GMP* (RIGAKU Miniflex 600)
- **Single Crystal Diffraction** (Oxford Xcalibur)
- **Variable Temperature XRPD** (PANalytical X'Pert3 Powder)

### SPECTROSCOPIC ANALYSIS

- **FT-IR** (Thermo Scientific Nicolet iS 50) *GMP*
- **FT-RAMAN** (Thermo Scientific Nicolet iS 50) *GMP*
- **SSNMR** (Solid State NMR)



## Physicochemical Properties

### CHEMICAL CHARACTERIZATION

- **LC-MS** (Waters Aquity)
- **NMR** (Liquid State NMR)
- **ICP-MS** (Inductively Coupled Plasma Mass Spectrometry)
- **SEM -EDX** (Scanning Electron Microscopy)

### CHEMICAL PURITY

- **HPLC/UPLC** (equipped with UV, DAD, FLD, EC, RI)
- **Gas Chromatography** (Agilent 7820A)

### THERMAL ANALYSIS

- **Melting Point** (Mettler-Toledo MP70)
- **DSC** (Mettler-Toledo DSC)
- **TGA** (Mettler-Toledo TGA)
- **TGA-EGA** (TGA coupled with Nicolet iS 10 IR)
- **Hot-Stage Microscopy** (HSM)

### OTHER CHARACTERIZATIONS

- **Thermodynamic Solubility** (Avantium Crystall6)
- **Intrinsic Solubility** (Agilent 708-DS)
- **Dissolution Profile** (Agilent 708-DS)
- **pKa / LogP / LogD determination**



## Morphological properties

### CRYSTAL SIZE

- **PSD** (Malvern Mastersizer 3000) *GMP*
- **DLS** (dynamic light scattering)
- **SEM** (Scanning Electron Microscopy)

### CRYSTAL MORPHOLOGY

- **PLM** (Motic Microscope BA210)
- **Particle Shape/Size Distribution** (Malvern Morphologi G3)
- **SEM** (Scanning Electron Microscopy)
- **TEM** (Transmission Electron Microscopy)

### POWDER PROPERTIES

- **BET** (Micromeritics Gemini VII) *GMP*
- **Powder Rheometer** (Freeman FT4)



## Water content

### DVS

(Dynamic Vapour Sorption SMS Intrinsic)

### KF

(Mettler-Toledo Karl-Fischer)

### WATER CONTENT

(Berghof EasyH2O)

# Design & develop



ROUTE  
SCOUTING



PROCESS  
DEVELOPMENT



PROCESS  
IMPURITIES



OPTIMIZATION  
OF CPPS



IMPROVEMENT  
OF EXISTING  
PROCESSES

**AIM: Develop a reproducible, robust, scalable and efficient process in lab scale.**

up to 9 weeks



## Process Development

- Data mining to define a screening design
- Identification of parameters interactions
- Selection of Input Process Parameters



## Optimization of CPPs with DoE

- Fractional Factorial Design varying all factors
- Randomization of the experimental order
- Blocking to reduce the variables noise
- Replication to reduce variation masking
- Definition of ranges of key and CPPs



## Route Scouting

Collaborating with our Clients to to identify the most cost-effective and sustainable route as early as possible. Integrating the state of the art knowledge with our expertise



## In situ Sensors

- Particle size and count (FBRM G400 MT)
- FT-IR (ReactIR 15 MT)
- UV-vis (UV-Vis Cary50)
- Heat Flow Calorimetry (EasyMax102 HFCal)
- Temperature, Turbidity and pH



## Controlled Reactors

- Mettler-Toledo EasyMax (50 mL÷100 mL)
- Atlas Jacketed Reactor (50ml÷5L)
- Pressure Reactor (up to 5L)

# Manufacture



CUSTOM  
SYNTHESIS



SCALE UP



INTEGRATED  
TECHNOLOGY  
TRANSFER



KILO-SCALE  
MANUFACTURING



## Custom Synthesis

Our team can support you to **synthesize** any **challenging** molecules, from grams to **kilograms** by designing new synthetic routes ensuring high quality.



## Integrated Technology Transfer

We fully support our clients during the technology transfer, in order to **satisfy every requirement** by working closely with them thus **optimizing time** and **related costs**.



## Scale Up

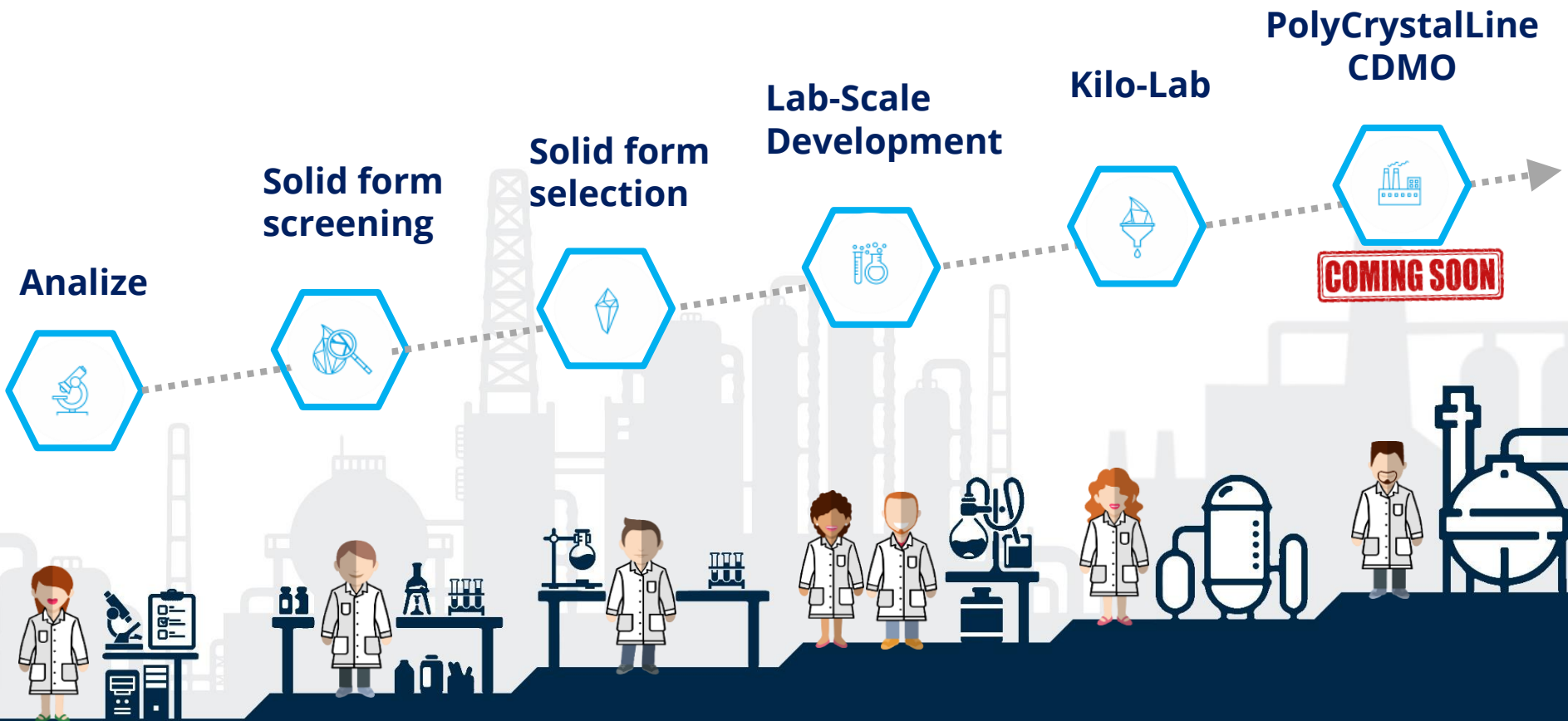
We offer efficient **development** and rapid **scale-up** of multi-step procedures. The use of automatic reactors guarantee the **monitoring** of all parameters.



## Kilo-Scale Manufacturing

We are equipped with Multi-purpose **Kilolab** units ideal to run experiments at kilo scale during **development**.

# Integrated Form Development



# CDMO DIVISION

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## Facility

A more than 8000 sq.ft.  
Brand new Facility built from scratch  
will be ready in the 2<sup>nd</sup> quarter of 2021.




## Location

Polycrystalline CDMO division will  
be located in Mesagne (BR),  
10 Km from the Brindisi Airport



## Production Scale



Polycrystalline CDMO division intend to be a contract manufacturing able to supply GMP certified multikilogram (up to 10 Kg) batches maintaining the same focus and expertise on the solid state chemistry.

The Aim of the CDMO division is to become a reliable partner in the production of semi bulk batches, guaranteeing a GMP quality in order to supply the desired API.

Our reactors scale will allow our partner to quickly access to the first GMP batch Of the API coming from our R&D laboratories.

## NEW FOCUS



### Fully integrated Tech transfer



Our solid state expertise gained in the historic facilities of Medicina (Bologna, IT) will be transferred to the new CDMO division, the client will have access to all the Polycrystalline facilities, integrating know-how, quality and instrumentations. This approach will prepare the full technology transfer to the client facilities.



### Genotoxic Impurities

Our quality system will be focused on the monitoring of genotoxic impurities (GTIs) which may be formed during the production. Thanks to a powerful network of collaboration we can guarantee a wide range of biological services aimed to the study and the identification so GTIs



## NEW CAPABILITIES

- **kilo-lab 1**, cascade 20L glass reactor + 50L glass reactor
- **kilo-lab 2**, cascade 50L glass reactor - 100L glass reactor
- **2 X 30L** glass pressure filter reactor
- **20 L** glass stand alone reactor
- **50 L** glass stand alone reactor
- **20 L** hastelloy stand alone reactor
- **glove box** fully equipped for the threatment of HPAPIs up to OEB4
- **micronizator**
- ..... and more to come



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An abstract blue graphic in the background of the top half, showing a network of glowing nodes connected by thin lines, resembling a molecular or data network.

## **EXPERTISE & QUALITY**

# SCIENTIFIC COMPETENCES



70% of PhD  
Scientists

## n.16 R&D Scientists

- Solid-State Chemistry
- Process Development
- Chemical Synthesis



# CERTIFICATED ANALYTICS



## Nr. 9 Lab Analysts

- Qualified Person
- Quality Assurance
- Quality Control



# CONTROLLED SUBSTANCES



We received the authorization from the Italian Ministry of Health to study physical and chemical properties of controlled substances.



# WE CAN WORK WITH HPAPIs



Up to OEB5

## Dedicated Isolators

- ITECO SGS 20 (Plexiglas)
- ITECO AMI (Stainless Steel)
- HEPA filters (H14) for input and output

OEL 100  $\mu\text{g}/\text{m}^3$

10  $\mu\text{g}/\text{m}^3$

1  $\mu\text{g}/\text{m}^3$

0.1  $\mu\text{g}/\text{m}^3$

OEB 1

OEB 2

OEB 3

OEB 4

OEB 5

Scale-Up/Optimization from 2 to 50 litres

Standard Hoods

Scale-Up/Optimization < 2 litres

Standard Hoods

Plexiglas Isolator

Stainless Steel Isolator

R&D/Analytical Services

Standard Hoods

Plexiglas Isolator

Stainless Steel Isolator

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**Transparent Partnership**

# MY CRYSTAL PRO

In **2015** we developed **MyCrystalPro**, our **online customer portal** that serves as a single source for **project management** and **communication**.

The screenshot displays the MyCrystalPro interface for the **Fenofibrate** project. The top navigation bar includes the PolyCrystalLine logo and the tagline "LET'S WORK TOGETHER!". The main header shows the project name "Fenofibrate", the project code "497128697", and the start date "28/11/2017". A sidebar on the left lists navigation options: Dashboard, Active Projects (selected), Archived Projects, Project label, My Meetings, My Inbox, My Calendar, Company info, Gantt Admin UI, Admin Tools, Clients, and Users. The main content area features a Gantt chart for the project timeline, with tasks categorized by status: TOTAL TASKS (6), IN PROGRESS (3), COMPLETED (1), and NOT STARTED (2). The Gantt chart shows tasks such as "MS1. Characterisation of current form" (100% complete), "Structural Characterization: XRPD, FT-Raman, and FT-IR (non-HP)", "Thermal Analysis: DSC, TGA, and EGA", "MS2. Solid form screening", "Evaporation: in single solvent and mixtures", "Slurry maturation: in single solvent and mixtures", "Precipitation: via anti-solvent addition, vapour diffusion, and cooling ramps", and "MS3. Developability and s". A "DISCUSSION BOARD" on the right shows messages from Antonella and Marco. The bottom right corner displays the user profile of Ciao Antonella, PHF SA, HEAD OF R&D.

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