

PolyCrystalLine

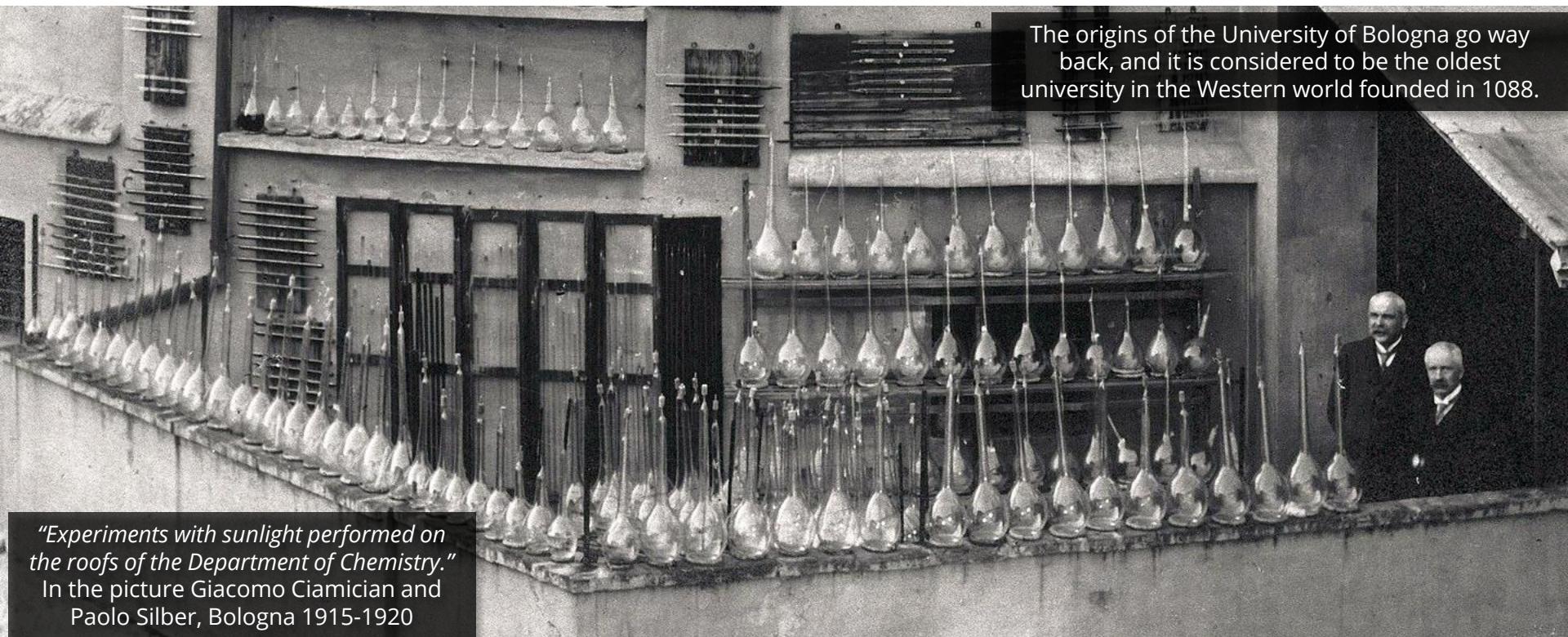
YOUR **INTEGRATED** SOLUTION PARTNER



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.

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 a 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.

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



"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

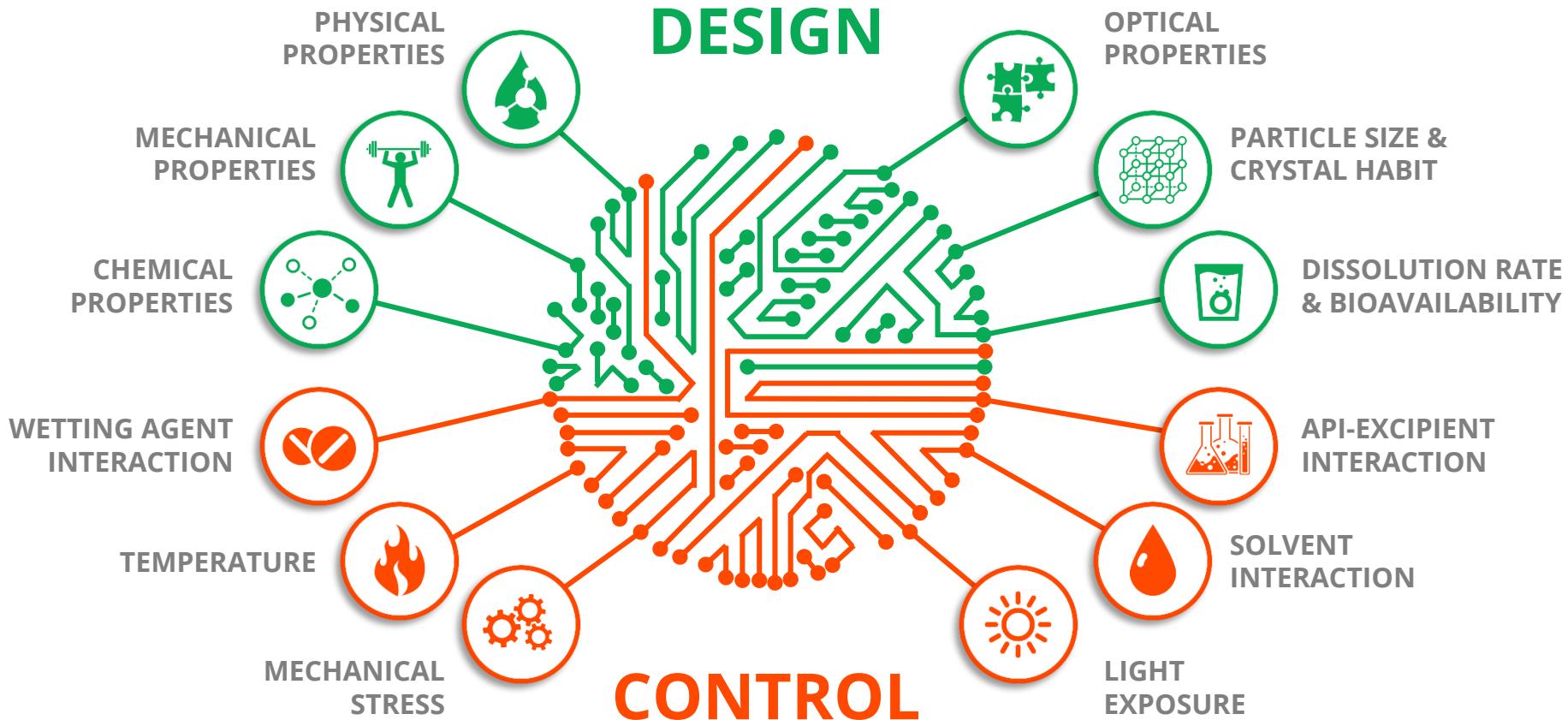


HOW TO PREPARE
any, as yet unknown,
crystal forms



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

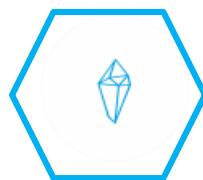
AIM: Identify and understand the most suitable form to move forward into development

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

Design & develop

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



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



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



Controlled Reactors

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



Route Scouting

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

Manufacture



CUSTOM
SYNTHESIS



SCALE UP



INTEGRATED
TECHNOLOGY
TRANSFER



KILO-SCALE
MANUFACTURING



Manufacture



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.

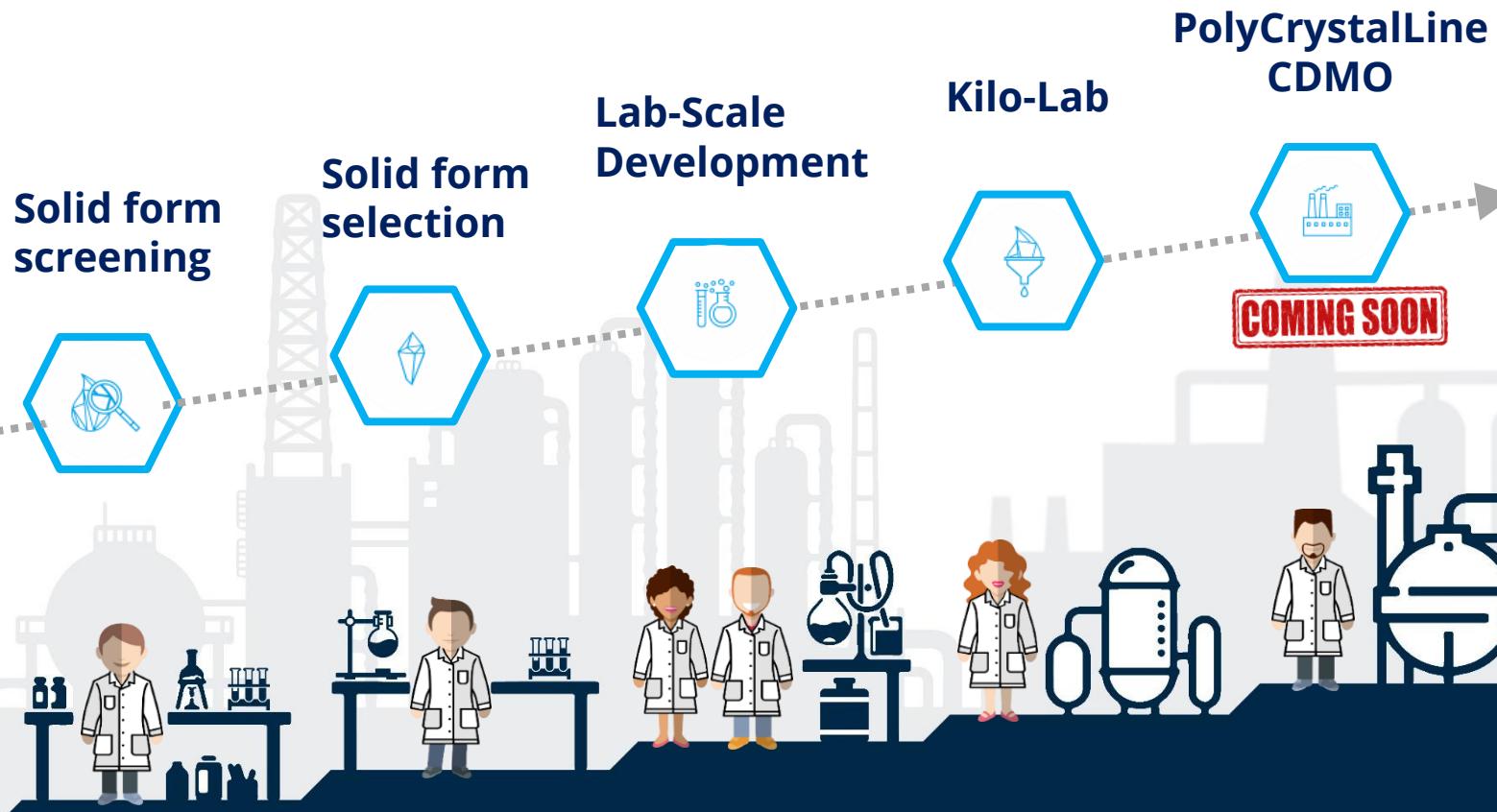


Kilo-Scale Manufacturing

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

Integrated Form Development

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CDMO DIVISION

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Facility

A more than 8000 sq.ft.
Brand new Facility built from scratch
will be ready in the 2nd 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

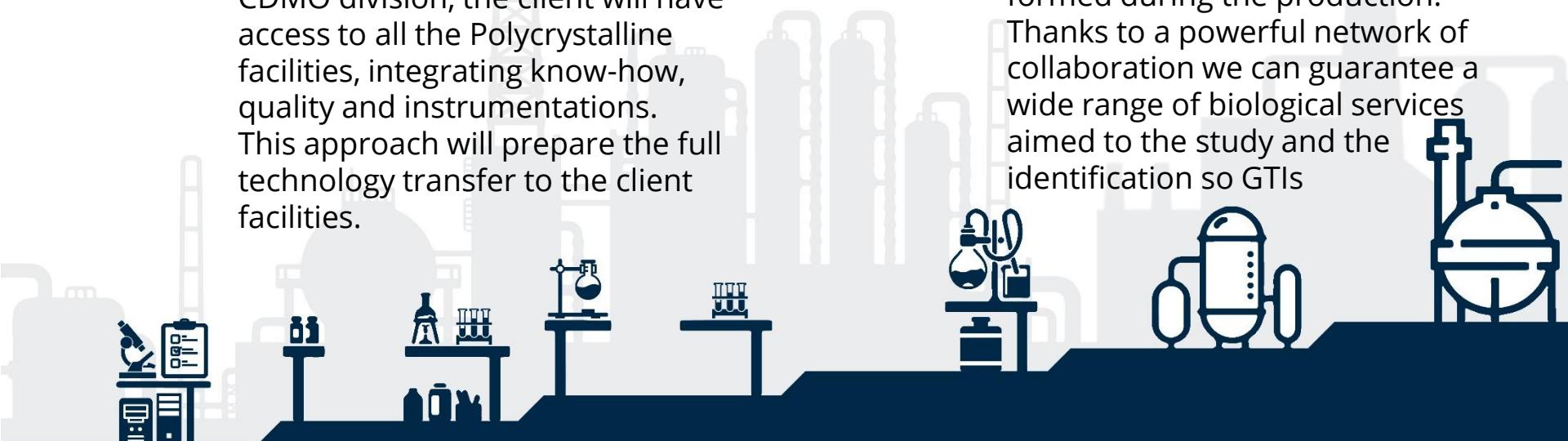


Our solid state expertise gained in the historic facilities of Medicina (Bologna, IT) will be transferred to the new CDMO division, the client will have access to all the Polycrystalline facilities, integrating know-how, quality and instrumentations. This approach will prepare the full technology transfer 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 treatment of HPAPIs up to OEB4
- **micronizer**
- and more to come



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EXPERTISE & QUALITY

SCIENTIFIC COMPETENCES



70% of PhD
Scientists

n.16 R&D Scientists

- Solid-State Chemistry
- Process Development
- Chemical Synthesis

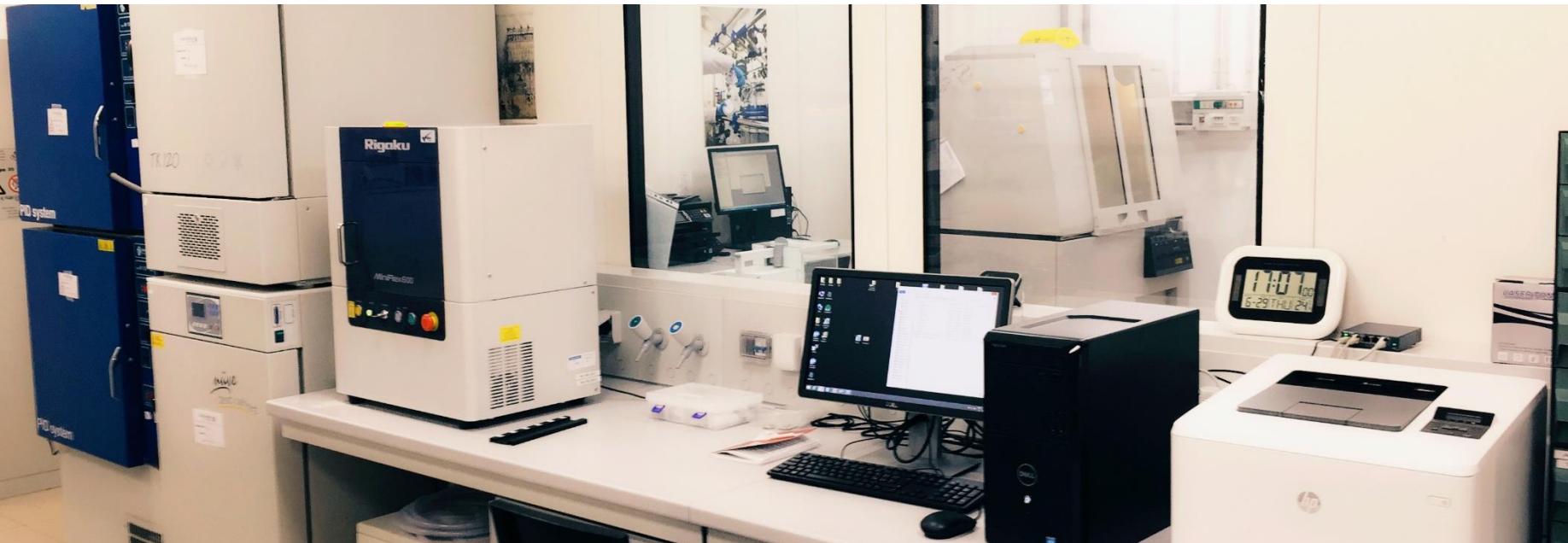


CERTIFIED ANALYTICS



Nr. 9 Lab Analysts

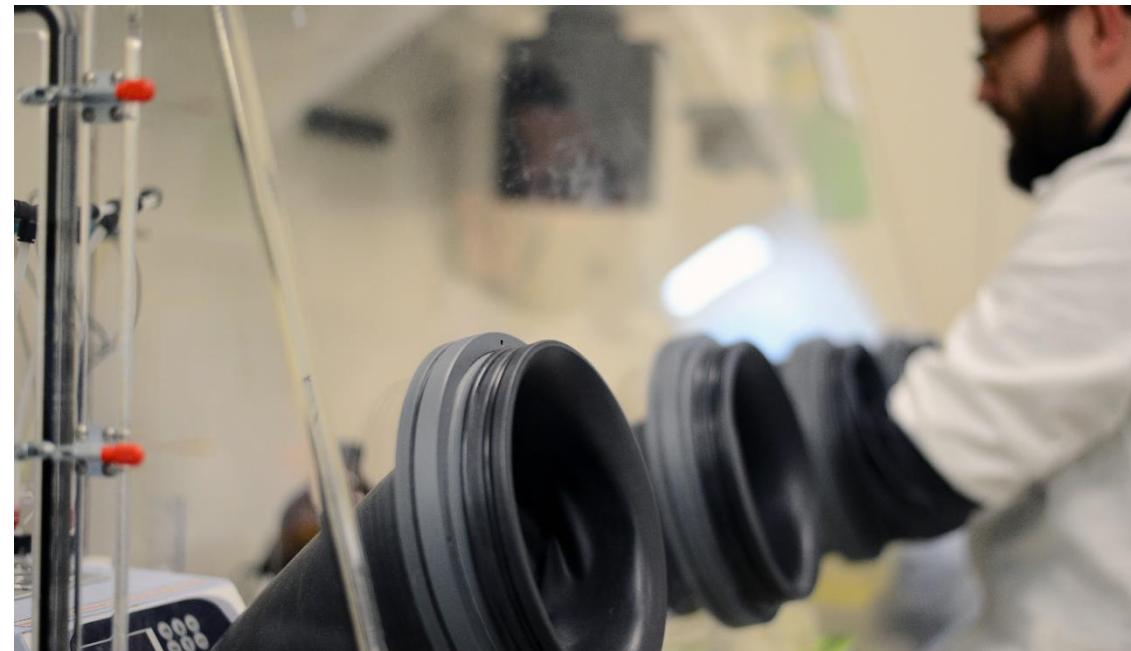
- Qualified Person
- Quality Assurance
- Quality Control



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 µg/m³

10 µg/m³

1 µg/m³

0.1 µg/m³

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**.

MyCrystalPro
LET'S WORK TOGETHER!

Fenofibrate

Project Code: 497128697 | Start date: 28/11/2017

Head of R&D: Enrico Modena (Polycrystalline)

Head of R&D: Bud Tamion (Arris)

Discussion Board:

- Ciao Antonella (PHF SA, Head of R&D) - Tue 08:23:15: Please inform us about the last TC scheduled.
- Marco - Tue 08:27:09: It was on Monday.

Enter message

TIME SHEET DOCUMENT 0 TASKS 5 PROJECT TEAM 11 REQUEST A MEETING

December, 2017

MS1. Characterisation of current form (100%): Structural Characterization: XRPD, FT-Raman, and FT-IR (non-HP)

MS2. Solid form screening (100%): - Evaporation: in single solvent and mixtures; - Slurry maturation: in single solvent and mixtures; - Precipitation: via anti-solvent addition, vapour diffusion, and cooling ramps

MS3. Developability and s...

Dashboard Active Projects FENOFIBRATE ACETAMINOPHEN CELECOXIB Archived Projects Project label NEW My Meetings My Inbox My Calendar Company info Gant Admin UI NEW Admin Tools Clients Users

TOTAL TASKS: 6 IN PROGRESS: 3 COMPLETED: 1 NOT STARTED: 2

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PolyCrystalLine S.p.A.

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