

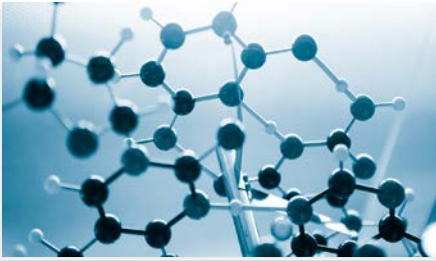


Olon acquisition of Infa: much more strength in CDMO

17 May 2017



olon ... *a partner
supplier*



A “new” company in the Market



- ✓ Established in 1907
- ✓ 5 Production sites in Italy
- ✓ Strong position in API production and Fermentation



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- ✓ Established in 1955
- ✓ 3 Production sites (2 in Italy and 1 in Spain)
- ✓ Strong position in CDMO and API production



A “new” company in the Market



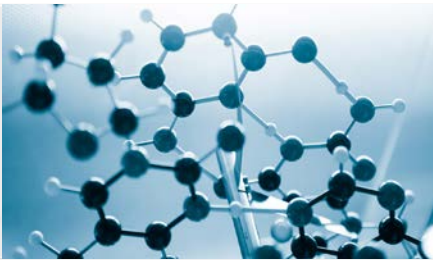
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May 2016 -> Acquisition of Infa Group by Olon

January 2017 -> End the Integration



THE NEW COMPANY AT A GLANCE

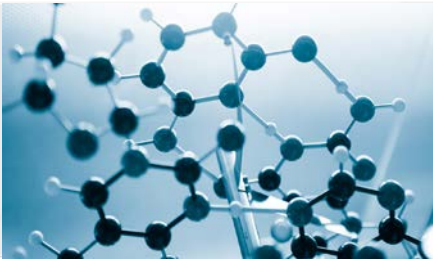
OLON S.p.A. is an European Contract Development & Manufacturing Organization offering **cGMP** Advanced Intermediates and Active Ingredients for the Life Science Industry.

- ❑ More than **1,300 people**
- ❑ About **400 Mio\$** turnover (2016)
- ❑ **5,340 m³** reaction capacity
- ❑ **33 Chemical Intermediates** (under Contract Manufacturing agreement) and about **200 APIs** (31 under Contract Manufacturing agreement)
- ❑ cGMP expertise, about **130 active US DMFs** and 50 granted CoS
- ❑ **8 European production sites** (Rodano, Settimo T.se, Garbagnate M.se, Mulazzano, Dorno, Segrate, Lodi and Murcia), all regularly **inspected by the FDA** and the designated National Health Authorities
- ❑ Headquarters in Rodano (Milan) (IT) and 3 branch offices to assure a solid service network: Hamburg (D), Parsippany NJ (US) and Shanghai (China)



Strengthened Technologies

- **Production of HP API: inhalation, CNS, cytotoxic anticancer**
- **Palladium Catalyzed Reactions**
- **Cryogenic reactions (down to -80 °C)**
- **Production and use of Boronic Acid**
- **Photochemical conversions**
- **Chromatographic purification**
- **Continuous flow chemistry**
- **High pressure hydrogenations**
- **Biocatalytic transformations (e.g. Ketoreductase)**
- **Witting-Horner reactions and modifications**
- **Synthesis of enantiopure compounds (resolutions, asymmetric synthesis)**



Cryogenic Equipments

Olon Segrate site

3,000 liters and **4,000** liters Hastelloy™ reactors

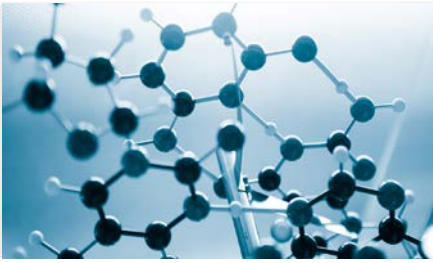
600 liters Hastelloy™ reactor under installation

Derivados Quimicos site

4,000 liters Hastelloy™ reactor

All of them are equipped with a cryogenic indirect cooling system with diathermic oil as temperature controlling fluid and using liquid nitrogen as primary cooling agent.

Operating range from -70/-80°C to 160°C



Cryogenic Equipments

Hastelloy™ Cryogenic Reactor



Cooling System

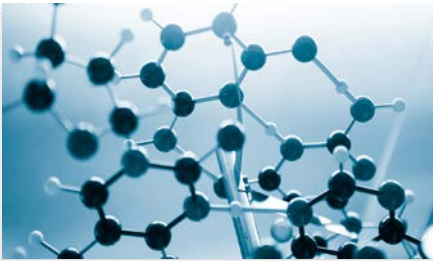




Cryogenic Technology

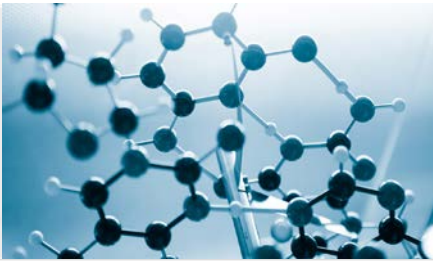
Type of reactions currently run under cryogenic conditions

- ✓ Stereoselective reduction of Ketones
- ✓ Chemoselective Halogen-Magnesium exchange
- ✓ Chemoselective Halogen-Lithium exchange
- ✓ Chemoselective deprotonation
- ✓ Chemoselective and stereoselective Grignard addition



Hazardous chemistry under cGMP

- Technology to handle hazardous chemistry under cGMP
 - ✓ Cyanuration
 - ✓ Bromuration
 - ✓ Large scale oxidations (e.g. H_2O_2 , HClO etc)
 - ✓ Hydride Chemistry Lithium Aluminum hydride and Borane complex up to hundreds of kg of active
 - ✓ Organometallic reagent such as Lithium Reagents up to hundreds of kg of active
 - ✓ Reactions with sodium metal (up to 150 Kg per production batch)



Fluorination A New Technology in Olon

Fluorination technologies

- **Corrosive, Toxic:**
 - ✓ Hydrofluoric Acid, Et₃N.HF.2HF, Py.9HF
- **Solid, Potentially Releasing HF:**
 - ✓ Amine Fluoride (TBAF – TMAF)
 - ✓ Alkali Metal Fluoride (KF, CsF, etc.)
 - ✓ Electrophilic Fluorinating Agents (N-Fluoropyridinium triflate, Selectfluor, etc.)
 - ✓ Deoxo-fluorinating Agents (DeoxoFluor, XtalFluor etc.)

All these Technologies Run under full cGMP



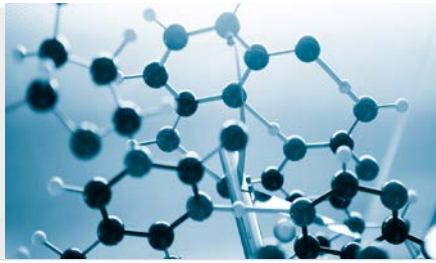
Fluorination A New Technology in Olon

From Lab Scale....

Teflon or PFA reactors installed

SOP for the handling of Fluorinating agent (except F₂)



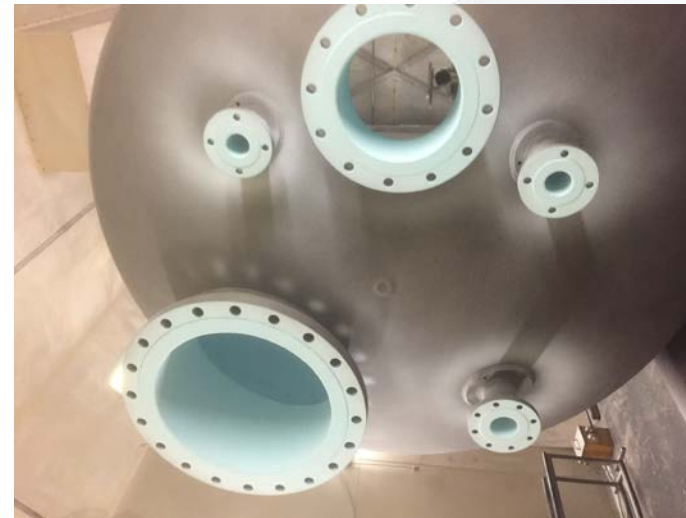


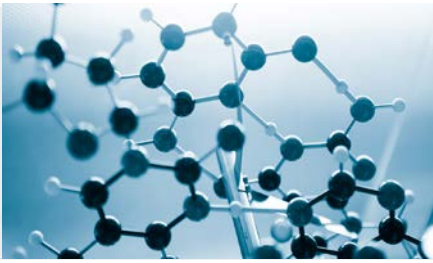
Fluorination A New Technology in Olon

.....To full scale

Two PFA coated reactors under installation:

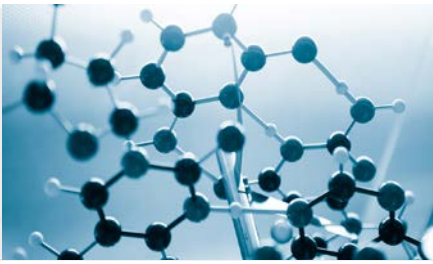
- R-109 600 L
- R-110 1,000 L





Olon Fermentation Technologies

- **Strain improvement and natural selection**
- **Genetic engineering**
- **Recombinant DNA technology with E.coli and yeasts strains (recombinant peptides)**
- **API and Enzymes preparation and Purification**
- **Fermentation processes parameters definition by DoE**
- **From flask up to pilot fermentation scale-up capability**
- **Beta-lactams, macrolides, lipopeptides and glycolipopeptides**



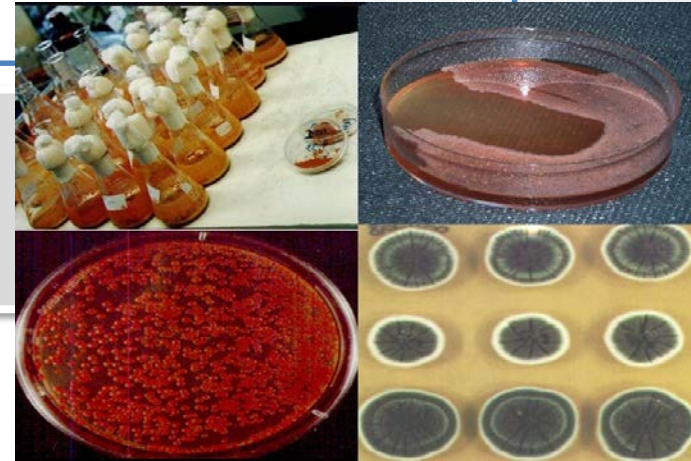
Olon Fermentation Technologies

Strain selection and improvement

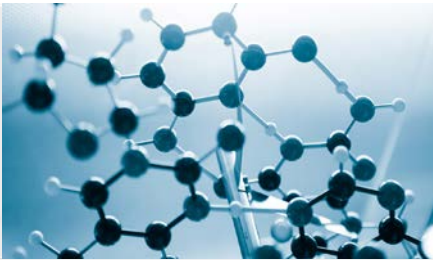
- Genetic engineering
- Mutagenesis
- Genome shuffling

Fermentation of APIs or Enzymes

- Batch, feed batch and partial harvest fermentations
- Product inhibition with resins
- Optimization with 'Experimental Design'

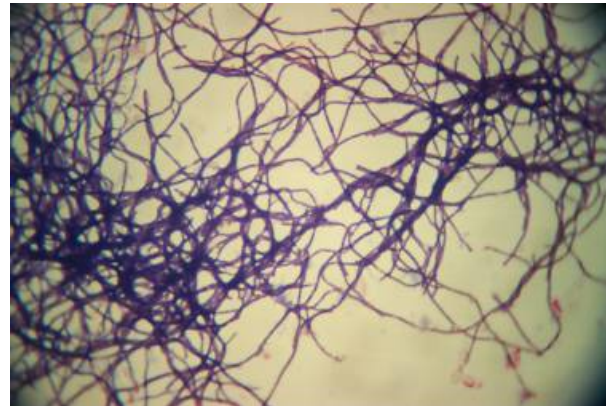


Preparation of Master Cell Bank / Working Cell Bank

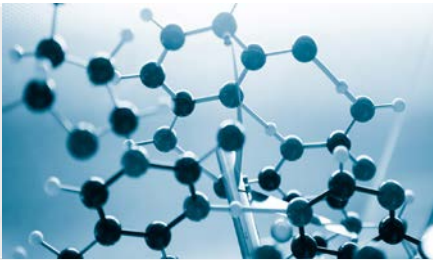


Fermentation R&D Facilities

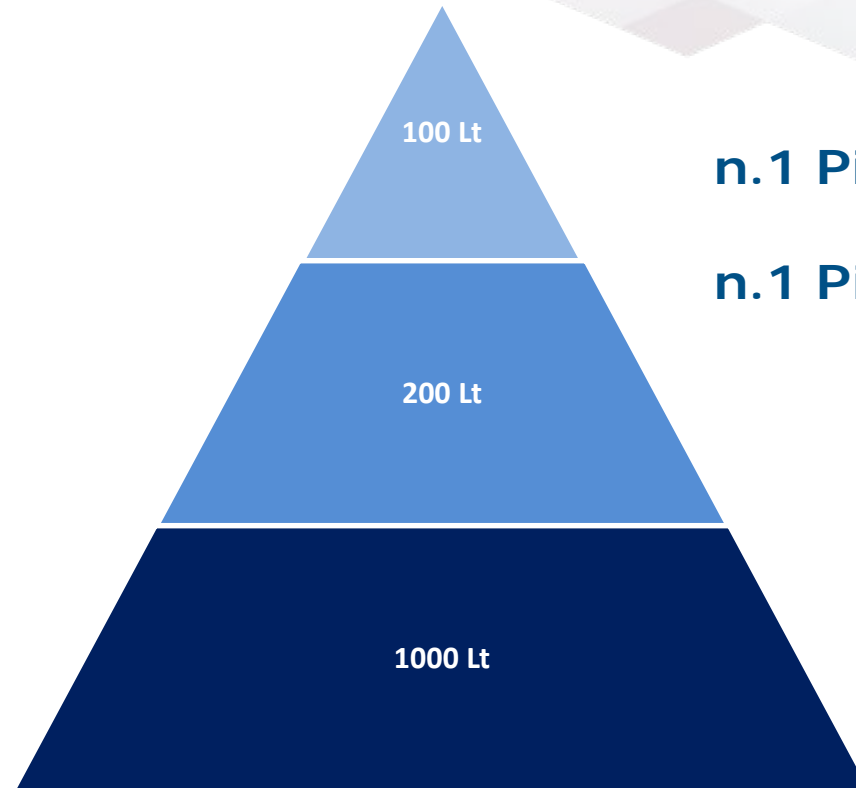
- 2 Laboratories for Strain Improvement
- 2 Laboratories of Microbiology



Macrolab with dedicated fermenters (20 L)



Fermentation Scale-up



n.1 Pilot plant for Fermentation

n.1 Pilot plant for Recovery



Biological Development (GMP): 21 dedicated fermenters and 5 sterilizers



Olon Down Stream Recovery Technologies

Wide range of modern technologies for:

- Filtration/concentration technologies (ultra, nanofiltration and microfiltration)
- Chromatography (several stationary phases and column shape)
- Finishing technologies (RO, dialysis, desalting, and additional purification technologies)



Olon Down Stream Recovery Technologies

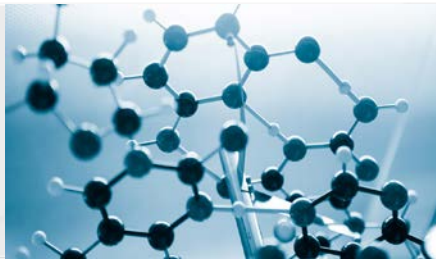
Secondary metabolites purification

- Centrifuges
- Membrane filter press
- Rotary pressure filter
- Microfiltration
- Ultra and Nano Filtration, Reverse Osmosis
- (Chromatography equipment up to about 3000 L)

Enzyme purification

- Cell lysis (mechanical homogenizer, with different chemicals, chemical flocculation)
- Permeabilization
- Clarification
- Ultrafiltration
- Chromatography





Olon Down Stream Recovery Technologies

Fully automated lines dedicated to APIs recovery from fermentation broth

MAIN EQUIPMENTS LIST:

Harvest/Microfiltration/Nanofiltration Unit

Broth storage tanks up to 150 m³,
Broth microfiltration performed with **Vibrating Pall membranes** (surface up to 600 m²)
Nanofiltration units up to 1200 m²

Chromatographic Purification

4 stainless steel columns from 2,2 to 9 m³ (800÷3200 l of resin bed)

Finishing Ultra/Nanofiltration unit

1 Ultrafiltration hollow fiber unit (72 m²), 2 spiral wounded Nanofiltration units (300 m² and 24 m²)

Freeze-drying unit

15 m² full automated Freeze Dryer, C grade (ISO8) Isolation clean room



High Potent Facility Highlights

- Occupational Exposure Limits (OEL) approach
- Glove Boxes for powders and closed lines for liquids
- Dedicated and isolated
 - production plant for High Potency APIs
 - warehouse for intermediates and finished products
 - QC laboratories
 - HVAC system and utilities
- Dedicated and skilled personnel
- Gases are treated and deactivated using dedicated scrubbers
- Wastes and Mother Liquors are segregated and off-site disposed by certified companies or they are chemically deactivated on site (when necessary)
- Waste water treatment plant



High Potent Cytotoxic Drug

Four Multipurpose lines - OEB5 ($<1\mu\text{g}/\text{m}^3$)
Containment

MAIN FEATURES:

- Glass lined reactors and stainless steel/hastelloy reactors (50 to 200 Lt)
- Operative temperature: -60 to $+100^\circ\text{C}$
- Chromatographic columns (60 to 100 Lt)
- Filter dryers Rotary and static vacuum dryers
- Continuous flow photochemical reactor
- Handling in Glove Boxes





High Potent Multipurpose Plant



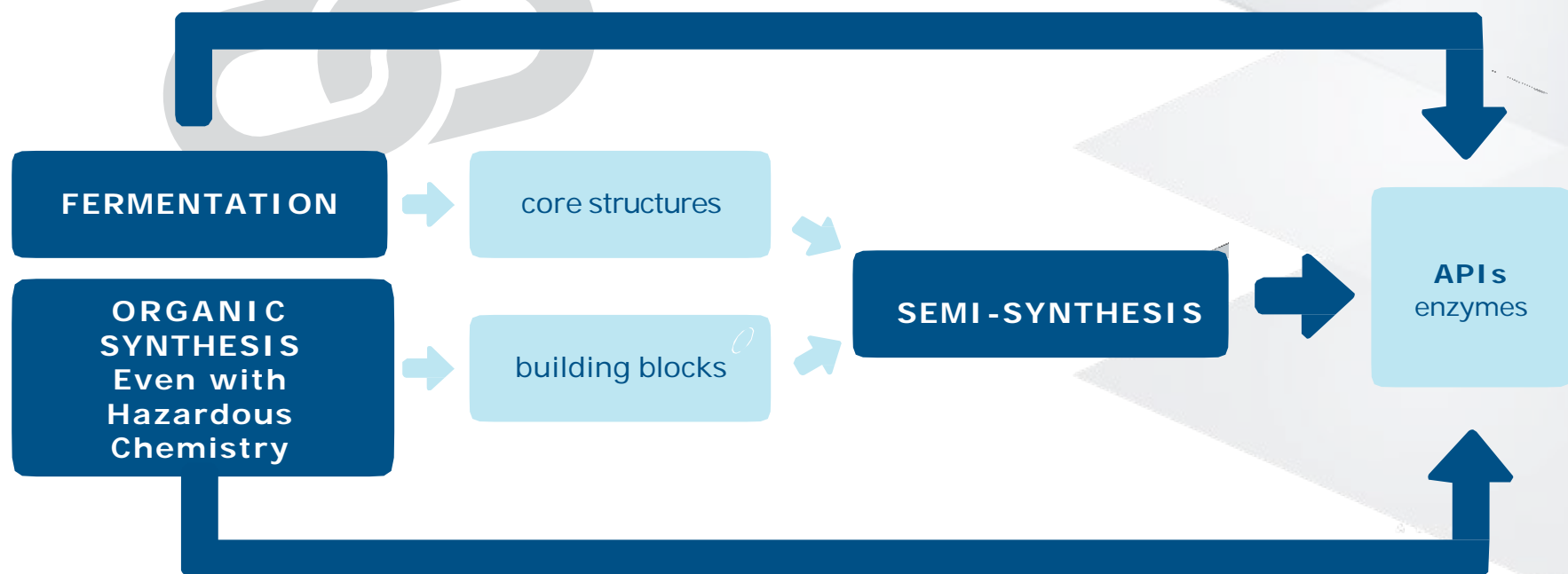
- 2x5 Litres reactor operating OEB 5 ($< 1 \mu\text{g}/\text{m}^3$)
- 1x15 and 2x20 Litres reactors operating OEB 3 ($10\text{-}100 \mu\text{g}/\text{m}^3$)





CDMO

Olon demonstrates how **fermentation** and **chemical synthesis** can be combined to produce APIs of interest to originators searching for new molecules.

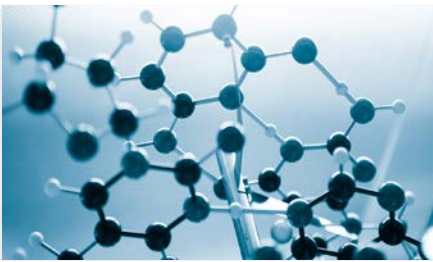




ADDED VALUE: R&D

EXPERTISE

- **110** qualified people make a highly experienced R&D team
- **Fully equipped analytical R&D lab** to support the R&D activities (NMR, Q-TOF LC/MS, Triple Quadrupole LC/MS, GC/MS, GCs, HPLC, UPLCs)
- **DoE** approach and **Parallel Synthesis Capability**
- Process development toward efficient industrial productions (**from hundred grams to tons throughout all Clinical Phases**)
- Process scale up optimization through
 - ✓ **6 cGMP pilot plants** (synthetic and semisynthetic chemistry)
 - ✓ **3 cGMP kilolabs** with high containment
 - ✓ **1 cGMP fermentation pilot plant** and **1 cGMP recovery pilot plant**



ADDED VALUE:

PROCESS SAFETY STUDIES

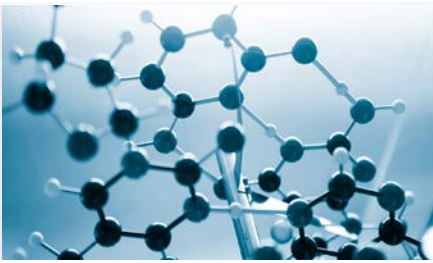
- ❑ A dedicated laboratory for Process Safety Assessment
- ❑ Thorough process safety evaluation
 - Hazard assessment at lab scale within R&D team
 - ➔ early stage process optimization opportunities
 - Safety evaluation at full scale production
 - ➔ joined team: R&D, plant manager, EHS manager



OLON owns dedicated equipments:

- ✓ Reaction calorimeter
Using different instruments we can study reactions from -30°C to 160°C and up to 6 bar (e.g. hydrogenation)
- ✓ Adiabatic Calorimeter
Stability of substances and reaction mixtures, gas release
- ✓ DSC
Thermal stability of pure substances and reaction mixtures



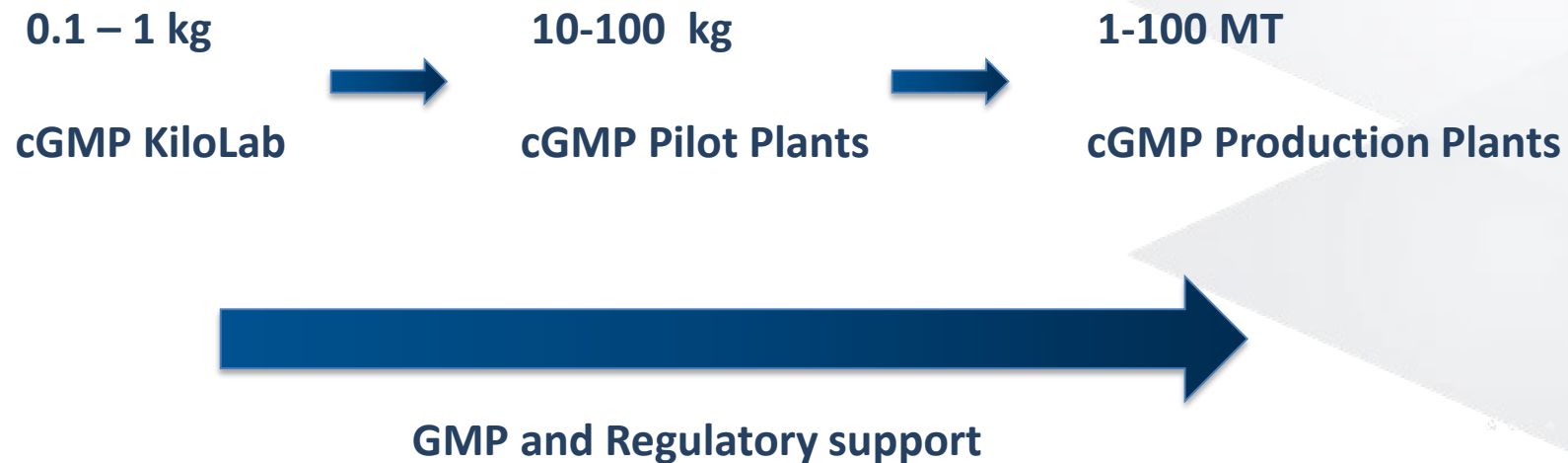


Combined Active projects

26 Active Projects to final API supporting New filing

23 Active Projects on Late Intermediates for New Chemical Entities

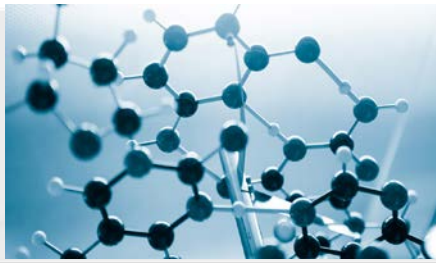
12 Active Projects to Final API as New Chemical Entities





A “Stronger” company in the Market

The acquisition of Infa by Olon creates a new Company that can offer full integrated packages and services to support the full development of API (from grams to MultiTon) based on Olon strong knowledge in both Chemical and Biological process all of them under a full cGMP and regulatory coverage



Visit us at our Booth # 1301



thank you