Master's Program 2021-2022 in

Process Chemistry applied to active pharmaceutical ingredients

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Module 1: Drug Discovery and Development: An Introduction to the Industry **10 hours**

Speaker: **Pietro Allegrini**

History of Pharmacy
How drugs are discovered and developed (with case studies)
Current practices in marketing
Drug lifecycles
How drugs are manufactured
Patented drugs vs. generics
Future trends

Module 2: API Regulatory Concepts and analytical techniques **30 hours**

Speaker: **A. Bortoli – C. Gaiarin** **20 ore**

Introduction to the Pharma Industry and definition of Drug Regulatory Affairs
General principles of International Pharmaceutical Law
International Marketing Authorizations
Development of Pharmacological and Toxicological documentation
Highlights of Clinical Documentation
Development of Chemical and Pharmaceutical documentation:

- API quality standards, with focus on ICH Quality guideline portfolio
- API safety standards, with focus on ICH Safety guideline portfolio
- Multidisciplinary topics impacting quality and safety (e.g. genotoxic impurities)
- GMP concepts and facility auditing

Marketing strategies, line extensions, pharmacovigilance

Speaker: **F. Panarotto** **10 ore**

Survey of techniques used in Pharmaceutical Development (to be elaborated)
Method development and validation
Process analytical technology (PAT)
Quality by Design
Analytical characterization of APIs for filing

Module 3: Intellectual property and Patent Law **20 hours**

Speaker: **M. Valle**

Definition of intellectual property and industrial property; patent rights as industrial property rights.
Historical excursus on patent law.
Difference between patent rights and industrial secrets.
Term and territoriality of patents.
Patents as an object of property (right to obtain a patent: ownership and inventorship) – Licenses and transfers of patents.
Exclusive rights conferred by patents and limits to the exclusive rights (experimental exemption, Bolar exemption…)

Patentability requirements – Patentable and non-patentable inventions, with particular focus on chemical inventions.
Structure of a patent: requirements of the description and claims. Reading a patent as a source of technical information or in view of determining freedom-to-operate.
Overview on procedures for obtaining and maintaining a patent: filing and examination up to grant and post grant proceedings before patent offices.
Nullity proceedings and infringement proceedings before national courts.

Module 4: ***Equipment, safety evaluation and cost analysis in the industrial manufacturing of APIs*** **30 h**

Responsabile M. Verzini:

speakers

M. Nebuloni + A. Barozza	**10 h**	**Safety in APIs manufacturing**
D. Pagani	**4 h**	**Machines and plants in API synthesis**
A. Tacchi	**4 h**	**Materials used in pharma industry**
P. Pretin	**4 h**	**Heat and mass transfer in organic reactions**
M. Verzini	**8 h**	**Cost analysis in APIs manufacturing**

Introduction: what is a process?
Material and energy balances
Phase behavior
Heat transfer theory
Mass transfer theory
The properties of fluids: flow and mixing
Reaction modeling: kinetics
Separation processes, from phase separation to chromatography
Process equipment design in APIs manufacturing
Particle engineering
Biochemical engineering
Thermal safety in the pharmaceutical plant
Operator safety
Environmental controls
Sustainability from an energy standpoint
Process economics and cost estimation
Description of important industrial processes in APIs manufacturing

Module 5: The Science of Crystallization **30 hours**

Speaker: R. Geertman (10 ore) + V. Colombo (8 ore) + C. Vladiskovic (8 ore) + N. Yazdapanah (4 ore)

Thermodynamics, solubility and supersaturation
Types of phase diagrams that are useful in organic chemistry
How a crystalline product (API or intermediate) is characterized
Polymorphism
Elements of crystallization process design
Theory of nucleation
Theory of crystal growth
Agglomeration
How to develop a batch crystallization

Analytical monitoring for a batch crystallization
Cooling crystallizations vs. anti-solvent additions
Continuous crystallization
Crystallization and impurities

Module 6: Process Chemistry in the Pharma Industry **50 hours**

Speaker: **40 ore tot: A. Manfredi (UNIMI, 8 ore), V. Farina (16 ore)**

+ P. Allegrini (6 ore), L. Cotarca (10 ore) + 10 ore flow chem (O. Kappe)

Flow chem
Introduction to the Pharma environment: what matters
Speed vs. cost
Route selection in early vs. late development
Reagent selection
Solvent selection
Optimizing reactions: mechanistic vs. screening approach
Control of adventitious impurities (water, oxygen, trace metals)
Unit operation development
How unit operations are run in the plant
Strategies for impurity control
Development of analytical controls (IPC)
Removal of PGI and metals
Process robustness and risk analysis
Process validation
Technology transfer
Commercial process troubleshooting

Module 7: Homogeneous Catalysis in the APIs synthesis **30 hours**

Speaker: **14 ore basic principles E. Gallo and A. Caselli (Unimi) + 16 ore V. Farina**

Basic principle of organometallic catalysis
Basics of physical organic chemistry applied to catalysis
The catalytic cycle: key parameters
Kinetics and. Thermodynamics
Techniques to determine kinetic parameters
Basic reaction steps that are important in organometallic catalysis
Understanding mechanistic details
Survey of major catalytic processes of interest to pharmaceutical chemists
How to develop catalytic reactions for the plant
Sustainable catalysis

Module 8: Chirality in Drug Design and Development **10 hours**

Speaker: **F. Sannicolo' (4 ore) + V. Farina (6 ore)**

Introduction to chirality; types of chirality
Biological consequences of chirality
Regulatory aspects of chiral drug development
Chiral switches

Production of chiral drugs

- Chromatographic methods
- Crystallization methods
- Synthetic methods based on natural synthons or templates
- Chiral catalysis

Case studies

Module 9: Biocatalysis in the Pharma Industry **20 hours**

Speaker: **T. Moody (10 ore) + S. Riva (10 ore)**

What is an enzyme?
Principle of enzyme kinetics
Genetic engineering strategies for enzyme optimization
Screening strategies
Major enzyme classes useful in organic synthesis
Survey of reactions used in organic biocatalysis
How to develop enzymatic reactions for the plant
How to scale up enzyme production
How to scale up an enzymatic reaction

Module 10: Principles of Green Chemistry in Organic Synthesis **20 hours**

Speaker: **D. Passarella (Unimi) 8 ore + R. Bona 12 ore**

History and problem definition
Definition of green chemistry
The principles of green chemistry
Metrics of greenness
Solvent use and alternatives to traditional organic solvents
Auxiliary reagents, groups, catalysts
Recycling things (solvents, co-products, catalysts, metals)
Energy requirements
Renewability of materials
Waste disposal
Example of green vs. non-green processes

Module 11: Putting this all together: Important Stories in Drug Development **20 hours**

A. Leganza-A. Bassan (4 hours) + **J. Roletto** (4 hours) + **G. Razzetti** (2 hours) + **M. Stivanello** (2 hours) + **G. Bertolini** (2 hours) + **V. Farina** (4 ore) + **L. Cotarca** (2 ore Polimorphism)

Seminars on Special Topics – **60 hours**

S. Console (Particle engineering)	6 hours
C. Pozzoli (HPAPI)	6 hours
E. M. Martinelli (Natural products)	8 hours
Organocatalysis – Photocatalysis – PTC (**M. Benaglia**)	8 hours
Oligonucleotides **(to be announced)**	6 hours
C. Giordano (Studies of Process Chemistry)	10 hours
J. Roletto (Industrial Fermentations)	10 hours
S. Cappelletti (Peptides in industry)	6 hours