SEQENS

OUR SCIENCE FOR YOUR FUTURE

Lipids & polymers for Biovailability, and challenges raised by their industrialization

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Seqens overview

SEQENS IN THE WORLD

SEQENS is a **worldwide leader** in the development and production of active ingredients, pharmaceutical intermediates and specialty ingredients

International manufacturing platform with integrated end-to-end capabilities

State of the art science platform

>€1,4BN
Revenue

c.3,400
Employees

1,000+
Clients

24
Manufacturing Sites
(13 cGMP sites)

10
Countries

10 R&D
Centers

>300
Research scientists & experts
(130 PhDs)

>12,000 SQM
Lab surface

16 KILO LABS
up to 50 L
& 7 Pilot Plants

SEQENS AT THE GLANCE

Focus on Seqens' Pharmaceuticals activities

Key Figures

M€350
Revenue

c.1,700
Employees

700+
Clients

10
Manufacturing Sites
(13 cGMP sites)

Generic APIs BU

Extensive of catalogue of Proprietary APIs

- 200+ DMFs for commercial APIs

Innovative BU

Standalone services

- Route Scouting
- Genotoxicity
- Solid state design
- Analytical excellence

Custom synthesis (CRDO / CDMO)

Small molecule APIs
Development and manufacturing of APIs

Intermediates
cGMP and non-cGMP intermediates & RSMs

Drug Delivery Solutions

- GMP Lipids and Polymers
- Solutions for Bioavailability
- GMP lipids and polymers for API/RNA encapsulation

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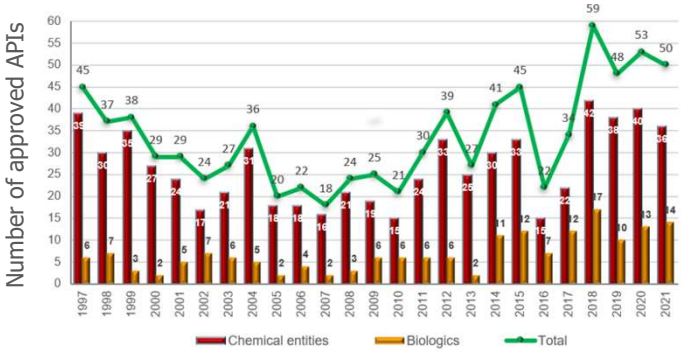
From Bioavailability issues to Drug failure

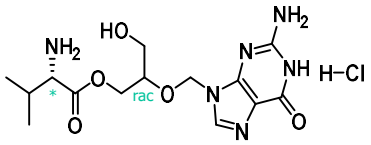
2

Size & complexity evolution of New Therapeutic Molecules over last decades (F.D.A.)

Fine-tuning the molecular design of APIs is required to enhance its binding selectivity for its biological target.
It is now common to observe new drugs weighting more than 800 Da, with multiple stereocenters.

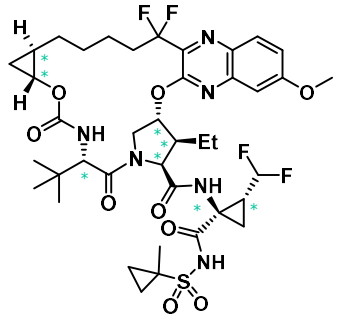


VALGANCICLOVIR
1 stereocenter controlled
M.W. = **390 Da**



2000 ROCHE

VOXILAPREVIR
8 stereocenters
M.W. = **868,9 Da**



2017 GILEAD

Year of Approval	1985	1995	2005	2015	2016	2017	2018
New Therap. Entity	40	35	25	44	22	46	51
New Chemical Entity	100%	90%	75%	66%	50%	72%	75%
Nber. of Chiral N.C.E.	12	12	10	15	9	18	23
% of Chiral N.C.E.	30%	34%	40%	34%	41%	39%	45%
Nber of resolved stereogenic center	**48**	**51**	**32**	**53**	**45**	**70**	**94**
Mean M.W. (Da)	405	419	392	489	571	533	492

- Small synthetic APIs still the major part
- New Therapeutic Entities become **more and more complex**

2

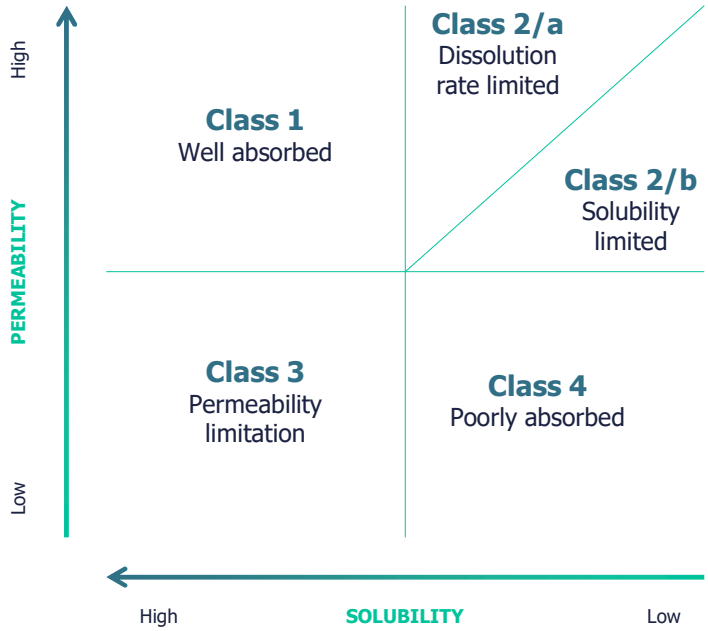
More and more complex Drugs: challenges for formulators

- **Insufficient bioavailability/efficacy:**
  40% of drugs fail in preclinical trials due to bioavailability issues
- **Stability** and **toxicity** problematic (related to polymorphic forms)
- Difficult galenic **formulation** (linked to crystalline and morphological form)
- **Discontinuity** of development (due to lack of anticipation of bioavailaibility issues)

2 Bioavailability as a key challenge for drug development

> 2/3 APIs present a bioavailability challenge, 10 to 20% of them being classified as Class IV (DCS classification)
➡ absorption issues, first pass metabolism and elimination by kidneys.

Developability Classification System (DCS)



		Oral dosage form approach
Class 1	**High solubility, high permeability** Marketed 35%, Candidates 5-10% *Ex: Paracetamol, antipyrine, propanolol*	Simple solid oral dosage form
Class 2	**Low solubility, high permeability** Marketed 30%, Candidates 60-70% *Ex: Acéclofénac, Ketoprofen, Phenytoin, Danazol, Nifedipine*	Increase surface area: particle size reduction, solid solution/dispersion Or use solvents/surfactants
Class 3	**High solubility, low permeability** Marketed 25%, Candidates 5-10% *Ex: Cimetidine, Ganciclovir, Acyclovir*	Incorporate permeability enhancer
Class 4	**Low solubility, low permeability** Marketed 10%, Candidates 10-20% *Ex: Bifonazole, Amphotericin, Taxol, Furosemide, Ritonavir*	Combine II and III

How to improve bioavailability?

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Several strategies can be deployed to improve bioavailability

Solid state

Particle size reduction

- **Increase surface area**
- **Improve dissolution kinetics**

- Milling : Jet mill Hammer/knife mill, Cryo mill
- Continuous crystallization (Taylor Couette, CSTR, tubular reactors)

Screening and optimization of crystal structure activities

- **Improve physico-chemical properties**

- Salt formation (counter ion)
- Polymorph screen (metastable form,hydrates)
- Co-crystal formation (co-formers)
- Predictive tool XTAlpi (AI)

Delivery systems

Formulation/ Drug Delivery

- **Increase solubility/permeability**
- **Controlled release**
- **Cytotoxic reduction**

- Excipients: Lipids & Polymers
- Hybrid excipients lipids-polymers
- Innovative formulation devices: Hot Melt Extrusion

Pro Drug development

- **Increase permeability**
- **Increase solubility**
- **Protection from metabolism**

- PEGylation
- Prodrugs

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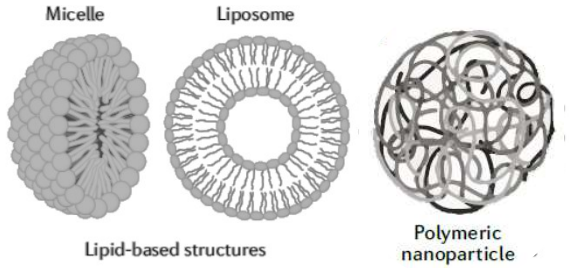
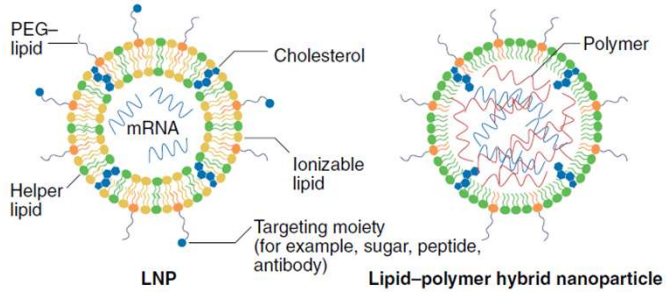
Drug Delivery excipients: Formulate drugs into Delivery Systems

A strategy to improve bioavailability is to formulate the drug with carefully selected excipients, such as **polymers** and **lipids**. These ingredients open up enormous customization and application potential, not limited to improving solubility.



Tremendous progress has been made in the design of targeted drug delivery systems, which **increase the selectivity** while **reducing the drug dosage**, thus **improving the risk-benefit ratio**.



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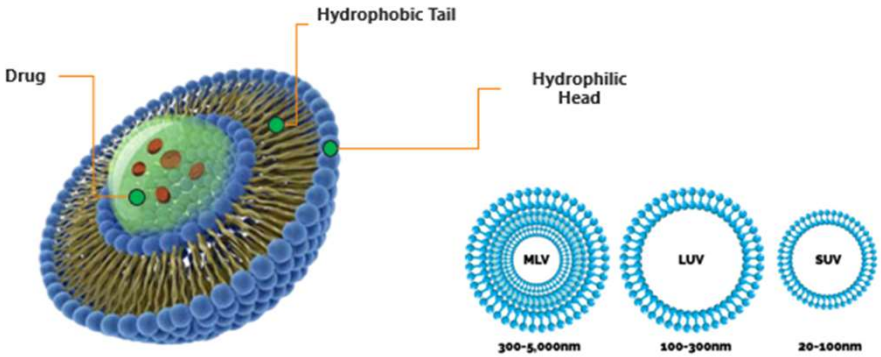
1. Liposomes are widely used in a variety of drugs

- Small artificial vesicles, consisting of one or more lipid bilayers
- **Biocompatible, biodegradable and low toxicity**
- Aptitude to trap hydrophilic and lipophilic drugs, demonstrated with several commercial formulations
- Lipids commonly used in liposome-based drugs: *Cholesterol, Cholesteryl sulphate, Triolein, HSPC, DSPE, DSPC, DOPC, DPPG, DOTAP, EPC, DOPS, POPC, SM, MPEG, DMPC, DMPG, DSPG, DEPC, DOPE*



Category	Application
In parasitic diseases	Liposomes are easily digested by phagocytic cells in the body and hence considered as one of the best vehicle to dispatch cargo into macrophages
Anticancer therapy	Liposomes are effective for the cells not only in tumors but also in the gastrointestinal mucosa
Other medical applications	Liposomes are sterically stabilized vesicles and are long circulating micro-reservoirs, or tumor (or site of inflammation and infection) targeting vehicles
In bioengineering	Fragments of siRNA and DNA are delivered with the help of modern genetic engineering and gene recombinant technology
In vaccination	Liposomes are considerably used in vaccinations due to their fine active targeting
In agro-food / Cosmetic industry	Due to its versatile physio-chemical properties lipids are extensively manufactured and used in large scale up sectors

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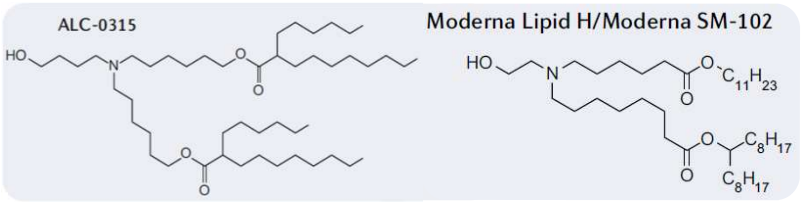
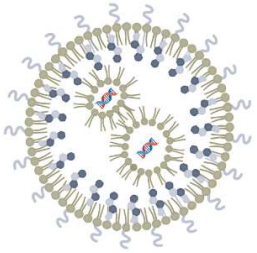
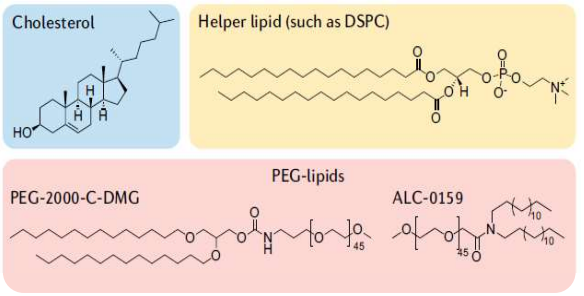
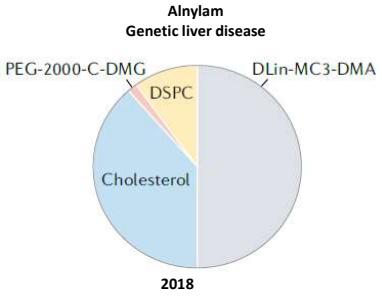
1. Drug Delivery Lipids/LNPs for nucleic acid delivery



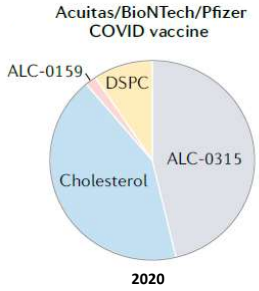




- **Non-viral vectors** to overcome the absorption barriers
- **Ionizable Lipid Nanoparticles** unlocked the potential of COVID-19 vaccines
- Hundreds of clinical trials have been initiated over the last two years to explore new indications in **oncology**, **vaccines**, immunology.



Patisiran : siRNA to inhibit transthyretine production (hereditary amyloidosis)



mRNA to produce spike protein

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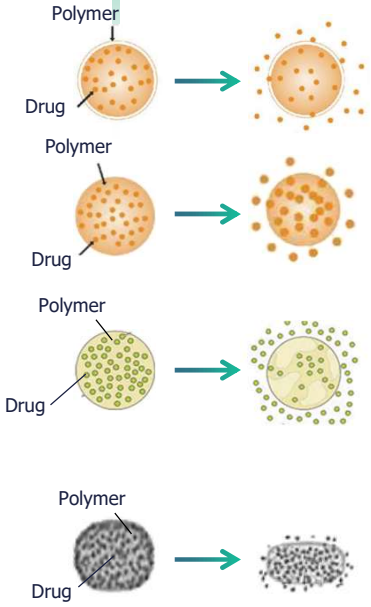
2. Drug Delivery Polymers

Hydrosoluble polymers (Polyethyleneglycol, Polyethyleneimine…, or copolymers thereof) and **Bioresorbable polymers** (PLA, PLGA, PCL), are widely used to encapsulate APIs or design API-polymers conjugates prodrugs mainly for **oncology**.

General Mechanisms of Drug Release from Polymers



Diffusion

Reservoir diffusion system

- The drug is contained in a core, which is surrounded by a polymer membrane and it is released by diffusion through this rate-controlling membrane
- Ex: poly(N-vinyl pyrrolidone); Poly(ethylene-co-vinyl acetate)

Matrix diffusion system

- The drug is released either by passing through the pores or between polymer chains, thus controlling the release rate
- Ex: polyethylene; polyvinylacetate

Degradation

- The drug molecules initially dispersed in the polymer are released as the polymer starts eroding or degrading
- Ex: PLA; PLGA; polyanhydrides, polyphosphoesters, polycaprolactone

Swelling

- These systems are initially dry and once placed in the body, absorb water or other fluids and swell
- Swelling increases aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the network
- Ex: N-isopropylacrylamide; ethylene-vinyl alcohol

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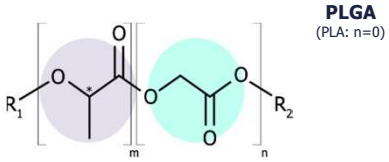
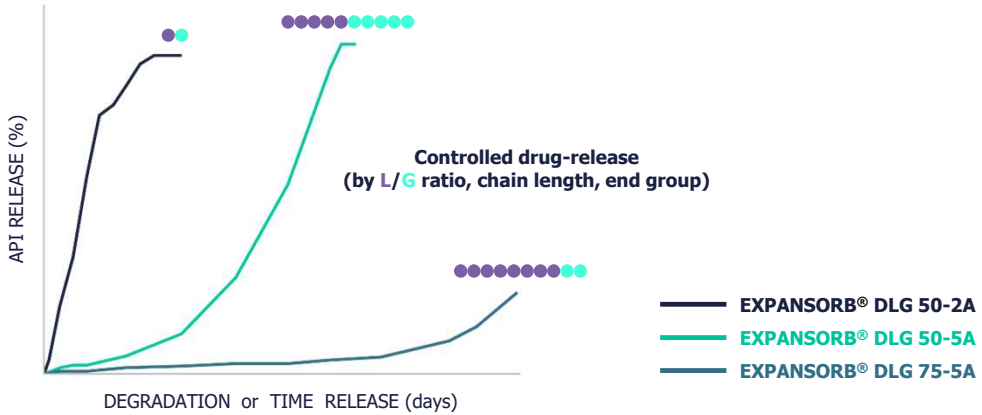
2. Drug Delivery - Bio-resorbable Polymers

Bioresorbable polymers such as PLA-PLGA or Polycaprolactone are used in controlled release drugs formulation for their ability to **protect APIs from degradation, reduce the number of intakes** and liberate the drug over a long period of time.



Example : PLGA

- **PLGA** (poly lactic-co-glycolic acid) is a **copolymer** of poly lactic acid (**PLA**) and poly glycolic acid (**PGA**)
- **Biodegradable :** PLGA is degraded through the hydrolytic cleavage of its polyester backbone. Degradation products, glycolic and lactic acid, are both non-toxic chemicals that can be metabolized by the body
- High level of parameters / performances tunability (L/G ratio, Mw, end-group…) to **monitor the release profile**
- **Highly biocompatible**
- Delivery vehicles for drugs, proteins and various other macromolecules such as DNA, RNA and peptides
- Long clinical experience, and several commercial formulations



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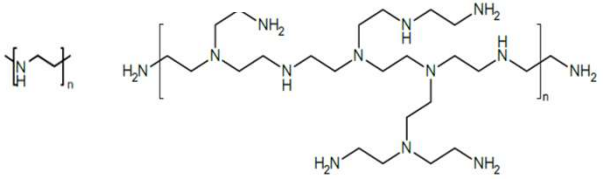
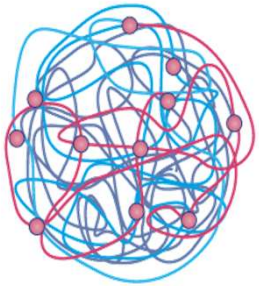
2. Drug Delivery – hydrosoluble Polymers for DNA/RNA encapsulation

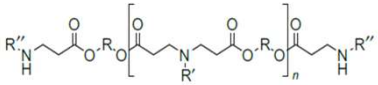
Cationic polymers for nucleic acid vectorization

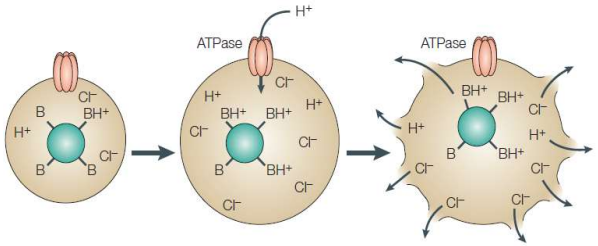
Linear and Branched PEI





PBAE





Example : Polyethylenimine PEI

- Cationic polymer with ability to stabilize RNA, studied in gene transfections since 1995
- **"Proton sponge"** properties : PEI absorbs protons in endosome → Cl content increase → osmotic pressure increase → endosome membrane permeation increases → mRNA release in the cytoplasme
  Physiological pH 7,4 > PEI pKa 7 > Endosomal pH 6,5
- PEI toxicity can be reduced with various strategies : partial acetylation, conjugation with PEG, HA, cyclodextrine…
- Low molecular weight PEI (2 kDa) demonstrate an ability to increase the nasal residence time of mRNA, to open the epithelial tight junctions, as well as an efficient transfection of dendritic cells
  → **potential as nasal delivery vehicle**
- Ability to be lyophilized and stored at +4°C

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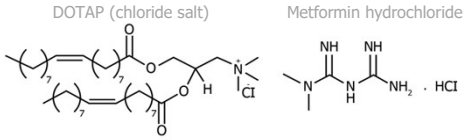
3. Prodrugs: conjugating APIs with Lipids or Polymers to improve their therapeutic potential

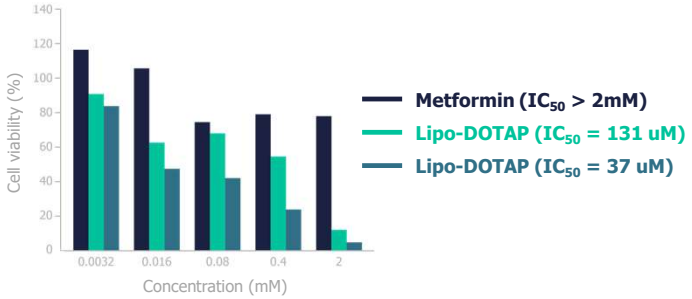
Chemical modifications on API enable to improve **permeability, solubility, reduce the cytotoxicity**, to give temporally **new interaction properties** (from a neutral to a cationic compound), enhancing the **pharmacokinetics** of the parent Drug.

Examples

Gaillard B. et al.; Chemistry: A European Journal, **2019**, 15662-15679

Chemical conjugation of **DOTAP and Metformin**, combined with therapeutic DNA plasmid, demonstrated a better in vivo effect than standard DOTAP-based nanoparticles.





Luo, C. et al, Biomaterials **2016**, 102, 239

4

Lipids & Polymers: industrialization challenges

4

Lipids & Polymers are complex molecules (multiple step chemistry) : appropriate methodology is required to optimize Costs & accelerate Time to Market

Challenges	Strategy	Solutions adapted to Lipids & Polymers
Optimize Production costs	Process optimization & robustness	**Multicatalysis** to decrease the number of chemical steps *High-Throughput Experiments* **Quality by Design** (analytics & process)
Time to market	Accelerate the supply of pre-clinical/clinical batches	Production capabilities from Early-stage chemistry (g scale) to large scale manufacturing (> 10s-100s kg) **Integrated CRDO/CDMO** approach
	Project management from early-phase to commercial phase	**Chemistry, Manufacturing and Control** Management ○ *Development/Scale-up* ○ *Regulatory filing*

4

The control of impurities in polymers & lipids is key to secure constant release properties as well as product safety

Challenges	Strategy	Solutions adapted to Lipids & Polymers
Product quality and Toxicology management	Product/impurities characterization	**Analytical methods development and qualification for impurity profiling, residual solvent analysis** High resolution LC-MS, CAD detector (lipids, no chromophore), RMN 500 MHz (polymers)…
		**Solid state characterization** XRPD (polymers)
		Nitrosamine assessment (NDSRI) HPLC-GC-HighRes MS (Orbitrap) coupling for ppb determination
		Bioinformatics/predictive models : QSAR **Tox assessment**: Cyto/photo/geno/embryotoxicity… Nano-AMES at early stage to reduce product quantity needs
	Remove impurities	**Purification technologies :** Filtration (polymers), chromatography (polymer, lipids), or alternative selective crystallization (salt screening for lipids)
Quality & Regulatory	Operate in the appropriate environment to ensure product safety, and compliance with Regulatory requirements	**GMP manufacturing** **Controlled-atmosphere manufacturing areas (ISO7)** for use of excipient in injectables formulations **Note :** regulatory guidelines for LNPs still under definition (current requirements close to APIs')

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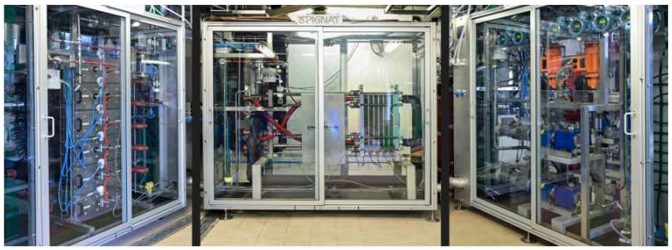
Lipid chemistry often involve energetic reactions and solvent consumption, thus requiring tight HSE management

Challenges	Strategy	Solutions adapted to Lipids & Polymers
Health, Safety & Environment	Ensure Process safety (control exothermy, pressure release…)	**Calorimetry studies, risk assessment** DSC-TGA, ARC = Accelerated Rate Calorimeter **Degradation & stability studies** **If required : Flow chemistry** (nitration, halogenation…)
	Reduce solvent consumption and wastes discharge (notably for chromato purification of lipids)	**Solvent optimization through Design of Experiment** Eventually: solvent recycling
	Protect operators, notably for Oncology Pro-drugs	**GMP Potent handling capabilities** for the conjugation of potent APIs and excipients



Hastelloy Coil reactors module | SiC Plate reactors module | Feeding module

4

Derisk all steps to increase clinical success rate and ensure product competitiveness over its whole Life Cycle

Challenges	Strategy	Solutions adapted to Lipids & Polymers
Clinical efficiency/ Bioavailability	Improve dissolution properties	**Solubility & permeability studies** *automated platform Inform: log P, pKa…* **Solid state characterization & optimization** **Particle size reduction and particle engineering (polymers)** *Micronization, milling* *Spray Drying* *Freeze Drying*
Generate intellectual property, and lengthen product Life Cycle (2nd generation)	Alternative routes of synthesis	**Innovative multicatalysis** **Biocatalysis** **Selective crystallization** – alternative to chromatography
	Alternative solid forms	**Polymorph screening** **Salt screening**
Secure industrial supply	Geographic derisking	**Vertical integration**: raw materials and intermediates **Double sourcing strategy**
	Purity of the raw materials	**Multiple suppliers qualification** **Purification methodologies** (chromatography, selective crystallization)

Conclusion

5

Lipids & polymers: a tremendous toolbox to improve Bioavailability and solve major therapeutic challenges

Efficiency

Targeted delivery

Toxicity reduction

IP Generation

Barrier to entry

With immense future potential:

Hypercholesterolemia : LNP/siRNA, as alternative to statins?
Hemophilia : LNP/mRNA to answer in situ protein (factor X...) deficiencies?
Polymers to pass through Blood Brain Barrier ? (Alzheimer disease…)
Development of oral route alternatives to parenteral ways of administration?

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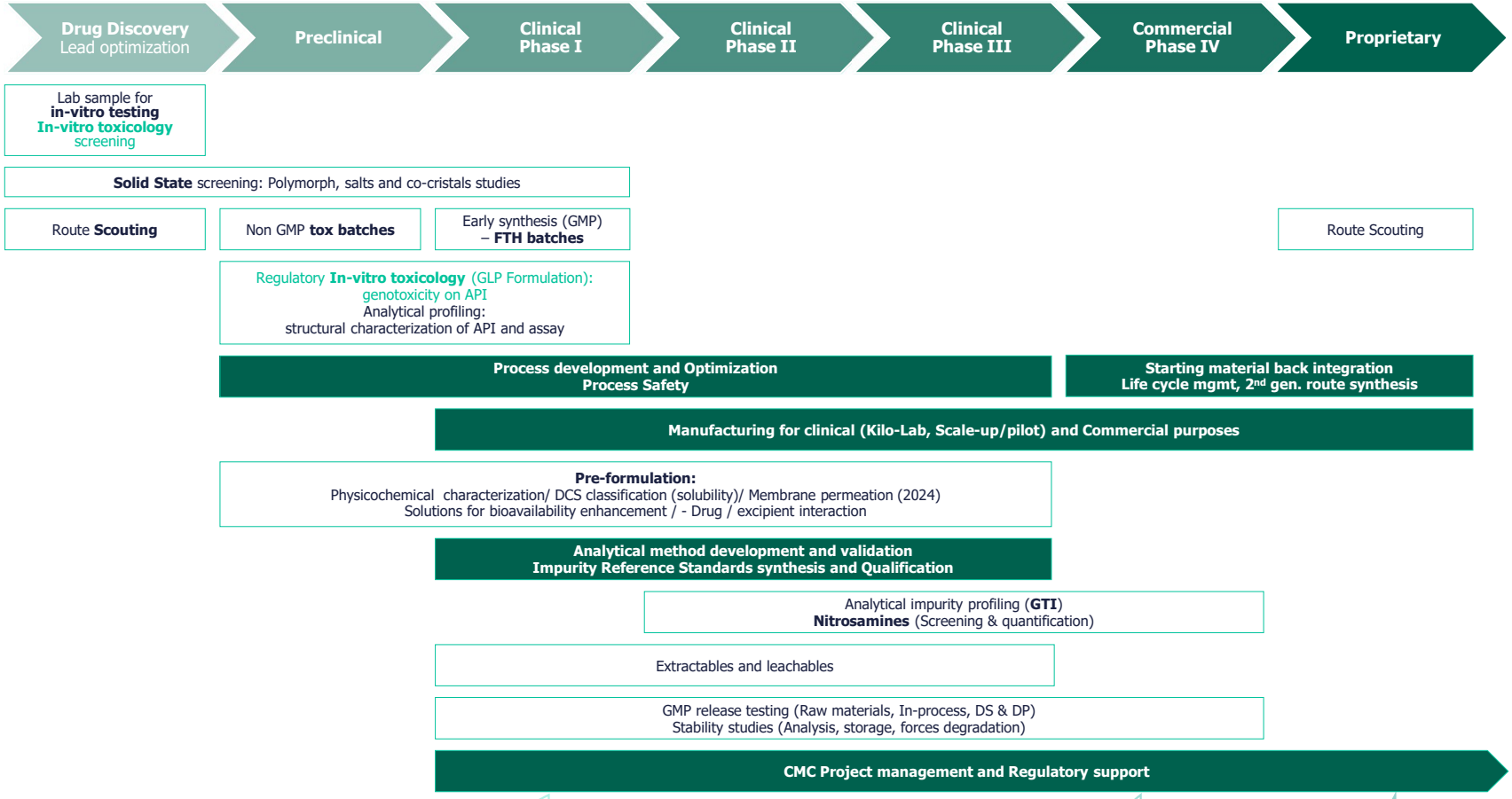
The development and supply of pharma excipients requires Chemistry, Manufacturing and Control competencies, similarly to APIs



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Seqens invests 15 m€ to build a new flagship multipurpose unit for cGMP polymers & lipids in Aramon (France)

CDMO services from clinical to commercial phase to provide a unique complementary GMP offer with ISO7 finishing:

- **Bioresorbable polymers**: PLA/PLGA, PCL
- **Hydrosoluble polymers/Copolymers**
- **Custom PEG/PPG**
- **Lipids**

For the target applications:

- **RNA Encapsulation**
- **Injectables**
- **Oncology**
- **Medical devices**
- **Bioavailability enhancement through PEGylation**

Timeline & Project

GMP equipments will be ready to deliver **Q2 2024**, and complement existing Seqens assets in US (Boston area) and Europe.

The project is supported by France Relance Program.

Thank you!

Frédéric Schab
Head of Business Development
Innovative CRDO
frederic.schab@seqens.com

SEQENS