Skyepharma

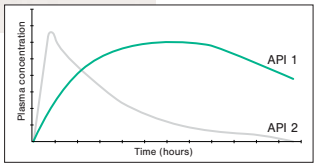
Expert and agile CDMO for classic
and complex oral solid dosage forms

CONTROLLED RELEASE TECHNOLOGIES

Three main proprietary technologies

Skyepharma is a leader in drug development and delivery of oral technologies serving the global pharmaceutical industry. Since it was founded, Skyepharma has had a strong focus on oral drug delivery, solving the many challenges of delivering the right dose of a drug to the right part of the gastrointestinal system for absorption at the right time and at the appropriate rate to achieve the desired therapeutic effect.

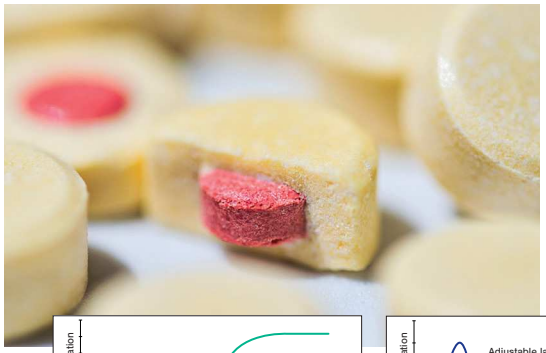
3 patented technologies; **Geomatrix®**, **Geoclock®**, and **Soctec®**. These platforms allow to build controlled release formulations to adapt to patient dosing schedules or adjust API intake. These technologies also allow to better manage side effects.

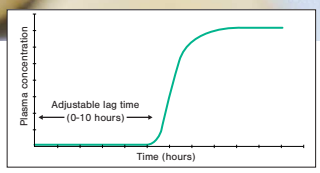


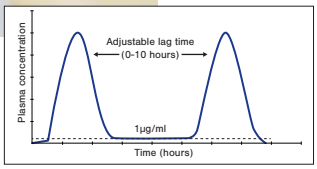
Geomatrix®

For short and large absorption windows

Geomatrix® is a well-established, validated and customisable oral drug delivery platform technology that is currently used in 8 products that are available in over 80 countries. Geomatrix® is highly versatile and can be applied to a wide range of different drugs to achieve a variety of different release profiles. It uses well-established ingredients and is easily manufactured using conventional production equipment.



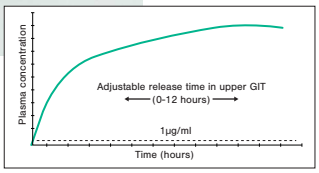




Geoclock®

Simple and double pulse. For a circadian treatment and to reproduce 2 IR administrations

Geoclock® is a validated oral drug delivery technology that can be used to release the drug from the tablet after a pre-determined lag-time and which is independent of food or pH. Geoclock® can additionally be used for multiple pulse delivery of one or more drugs with pre-determined time intervals between the pulses, or to target colonic release of drugs. Where more than one drug is included, the delivery profile can be different for each active pharmaceutical ingredient. Geoclock® is easily manufactured using conventional production equipment, minimising the need for capital investment.



Soctec®

For short absorption window

Soctec® is a versatile extended release gastro-retentive platform technology that has been designed to overcome many of the limitations of alternative systems. Skyepharma's Soctec® is designed to retain a drug in the stomach for an extended period of time so that it can be delivered in a controlled way to the duodenum and jejunum for subsequent absorption, so improving oral bioavailability and duration of action for sustained release formulations.

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DEVELOPMENT EXPERTISE

Formulation design and pilot process

Our expert team brings valuable expertise, helping our clients from early stage development to scale-up, Quality-by-Design and industrialization up to commercial manufacturing and packaging.

Our new product introduction department offers development and reformulation of classic and complex oral solid dosage forms for pharma and food supplement markets:

- Single layer tablet
- Multi-layer tablet
- Press coated tablet
- Capsules filled with powder, granules, pellets or tablets

DEVELOPMENT EXPERTISE

CDMO WITH
A CAPITAL “D”

Early stage development

FORMULATION

- Extensive experience in solving complex formulation challenges
- Advice on the best solution to optimize drug delivery for the benefit to the patient
- Application of proprietary technologies for modified release, pulsed release and delayed release
- Offer of additional IP protection to the product
- Early characterization of powders for anticipation of up-scalling issues
- Reformulation and troubleshooting

PROTOTYPING

- High quality prototyping with rapid screening of formulation options
- Manufacturing of technical or cGMP prototypes
- Small amount of API needed for small scale production
- Specific equipments: Procept, Styl’One evolution, MG2, Zanasi

Process development

Our expert team has significant experience in the optimization of complex formulations in order to ensure critical process parameters properly understood and controlled, and cost effective and robust processes at multiple scales.

SCALE-UP

Scale-up equipments: Aeromatic Fielder PMA and TSG2, Glatt GC 500/750

Quality-by-Design

Systematic and dynamic approach ensuring that quality is built by design from the early steps of development

- Derisked scale-up to commercial scale manufacturing with robust processes
- QbD realised with Styl’One evolution: using reduced amount of raw materials and API
- Statistical data treated using Minitab software

SKYEPHARMA’S QUALITY BY DESIGN METHODOLOGY

Global risk assessment on the whole process = determination of the most critical process step → **FMEA**

Determination of the potential CPP having an impact on CQA → **FTA**

Determination of the influence of each CPP on the CQA → **DOE**

PROCESS DESIGN SPACE

FMEA: Failure mode and effect analysis **FTA**: Fault tree analysis **CPP**: Critical process parameters **CQA**: Critical quality attributes **DOE**: Design of experiment

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MANUFACTURING AND MICROFLUIDIZATION

Extended capabilities in manufacturing

Skyepharma has a proven quality and regulatory track record and has shown remarkable manufacturing expertise for more than 25 years.

We aim at providing customized solutions, by offering flexible batch sizes, extended manufacturing and technology transfer capabilities for solid dosage forms.

Complete manufacturing solutions

At Saint-Quentin-Fallavier facilities, near Lyon (France)

GRANULES
Aqueous and organic solvent granulation
Roller compaction

TABLETS
Mono-layer, multi-layer and press-coated (tab-in-tab)

CAPSULES
Filled with tablets, granules, pellets or powder

DPI CAPSULES
Inhalation grade
100% online weight checked

IMMEDIATE OR CONTROLED RELEASE
Different technologies offered

FILM COATING
Tablets and capsules

BOTTLE PACKAGING
Plastic and glass bottle 100% automatic visual checking of tablets. Serialization and aggregation

BLISTER PACKAGING
PVC, PVDC, Aclar, Triplex/Alu and Alu/Alu. Serialization and aggregation

Microfluidizer™ technology

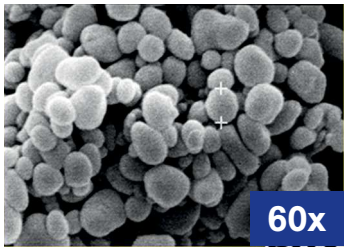
Biovailability enhancement for oral solid dosage forms

Microfluidizer technology is a dynamic high-pressure processing technology where the liquid solution or suspension passes through micro-channel(s) and is subjected to extremely high shear and impact forces to achieve uniform particle size reduction.

The obtained liquid solution or suspension is then spray dried to remove the solvents and produce the dried particulate system.

The use of exclusive fixed-geometry interaction chamber and unique way of scaling up through parallelizing multiple micro-channels guarantee the process scalability.

Before: 100 µm



After: 500 nm

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PACKAGING SERVICES

Skyepharma proposes a complete offer of packaging

Bottle packaging for all types of bottles

- Plastic or glass
- Cylindrical or square
- With or without desiccant
- With or without additional cotton
- All types of caps

Blister packaging

- PVC, PVDC, aclar, triplex/alu
- Alu/alu

The packaging activities complete our fully integrated offer which allow customers to have a single point of contact, from the early stages of project development up to commercial manufacturing and packaging.

Bottle line

Able to fill any type of bottle with tablets and capsules

PRIMARY PACKAGING (ISO 8)

- Plastic and glass bottles loading station
- Blowing station with clean air
- Tablets and capsules hopper
- Visual counting station with 4 inspection cameras
- Weighing cells before and after the filler head
- Automatic cottoning station
- Caping station (all types of caps)

SECONDARY PACKAGING

- Inductive sealer
- Rotary labelling machine including variable data printing and OCR
- Horizontal cartoner
- Track&Trace and labelling machine (Tamper Evidence)
- Automatic horizontal casepacker including aggregation camera and label
- Manual palletization and aggregation of the shipper case on the pallet

Blister line

Able to fill any type of tablet, capsule, in all types of blisters

PRIMARY PACKAGING (ISO 8)

- Forming station for both PVCs and aluminium
- All types of feeders for tablets and capsules

SECONDARY PACKAGING

- Horizontal cartoner
- Track&Trace and labelling machine (Tamper Evidence)
- Automatic horizontal casepacker including aggregation camera and label
- Manual palletization and aggregation of the shipper case on the pallet

Size and capacity

ROUND AND SQUARED BOTTLES

Up to 75 bottles/min.

Bottle width	18 to 90 mm
Caps's width	7 to 50 mm
Bottle height	35 to 180 mm

BLISTER

Up to 210 blisters/min.

Blister length	70 to 140 mm
Blister width	30 to 86 mm
Depth	Up to 12 mm
Materials	PVC, PVDC, Aclar, Triplex and Alu

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SERIALIZATION AND AGGREGATION

Skyepharma packaging lines for bottle and blister are both fully equipped for serialization and aggregation

- Packaging lines are connected to our Seavision site server which manages the serialization and aggregation data
- We connect quickly to our new customers via our multi-user platform
- Our system allows us to meet all regulatory requirements for all countries, particularly for the US, European, Russian and Saudi Arabian markets

SERIALIZATION AND AGGREGATION

INNOVATION AT
EACH PROCESS STEP

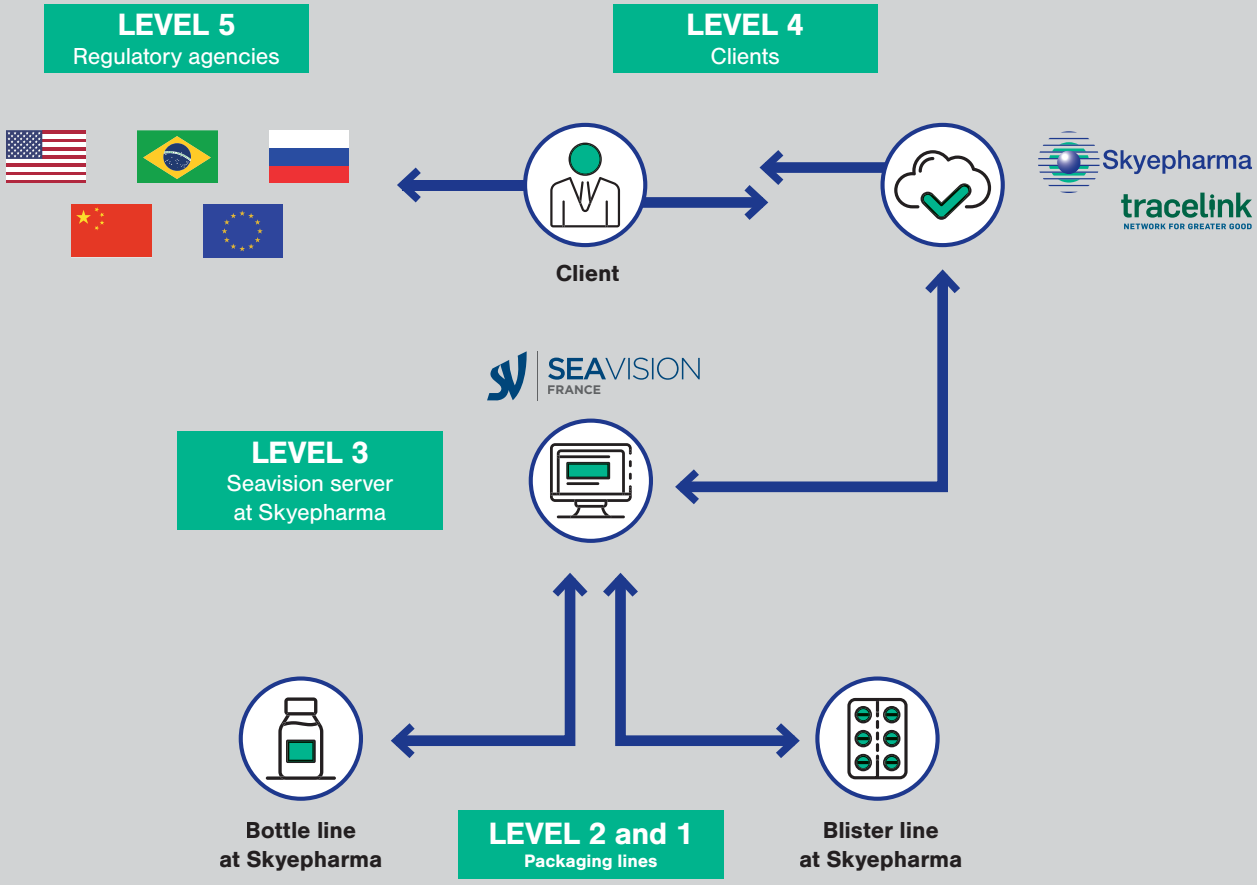
SERIALIZATION

Authentication on the carton with unique number.

AGGREGATION

The numbered cartons are linked to the case and finally to the pallets.

Skyepharma management system



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ANALYTICAL SERVICES

Analytical development

Product development is closely supported by a highly experienced team during every phase of the development process

- Analytical method development and validation
- Analytical method transfer
- Process optimization
- Registration and commercial stability studies
- Qualification of secondary standards
- Cleaning method development and validation

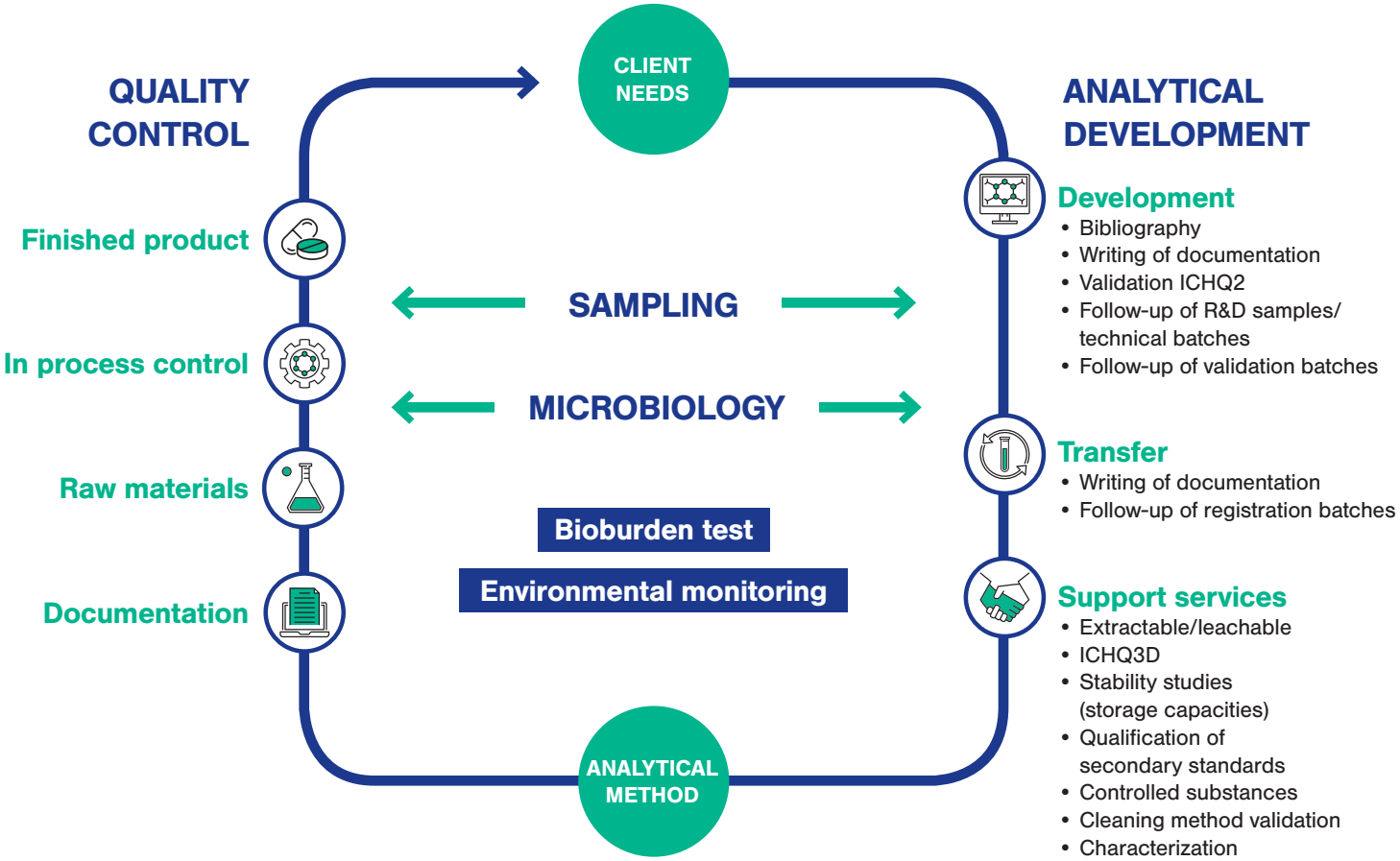
Quality control

Our dedicated QC team ensures the compliance of each excipient and API until the finished product

- Entire analyzes made according to the applicable pharmacopoeias or internal monograph
- Microbiological and chemical testing of raw materials, IPC and finished product
- Handling and analysis of controlled substances
- Handling and analysis of light-sensitive products
- Regulatory and documentation upgrade

From development to production

We prioritize agility and expertise, without compromising on quality



Laboratory equipments and capacities

IDENTIFICATION CHARACTERIZATION AND ANALYSIS

- Centrifugation for heat-sensitive products
- Surface area and pore size analyzer (BET)
- Friability, disintegration, viscosimetry, etc.
- Brookfield viscosimeter
- UV-Visible spectrophotometer (Perkin Elmer)
- IR/NIR spectrophotometer (Perkin Elmer)
- Karl Fisher (Mettler)
- Potentiometry
- Particle size analysis by laser diffraction (Malvern)
- Total organic carbon (TOC)
- HPLC/UPLC (waters and agilent): PDA multi-wavelength detector, UV detector, refractometer, mass spectrometer (Q-TOF)
- GC: FID e TCD detectors, headspace, gas valve
- On and offline dissolution (SOTAX)
- Mortar Grinder (Automatic)

SAMPLING AREA

- 20 Stability chambers
- Capacities
  - ICH conditions (25/60, 30/65, 40/75, 30/75 etc)
  - Refrigerated cond.
  - Freezer

MICROBIOLOGY

- Techniques
  - Bioburden tests (EP 2.6.12-13 / USP<61>)
  - Filtration method
- Equipments
  - Vitek® for germs identification
  - Autoclave (250 liter capacity)

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SUPPORT SERVICES

Skyepharma provides value across the whole supply chain by ensuring regulatory compliance and optimizing time to market

Skyepharma offers professional and experienced project planning, production and distribution scheduling throughout the product development and supply process.

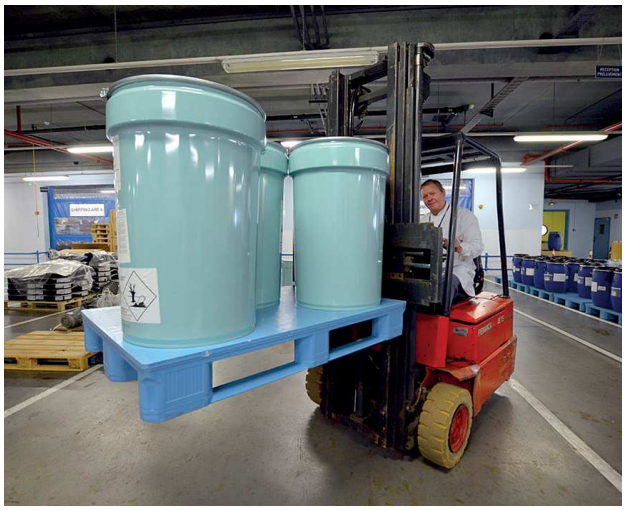
Our oral drug delivery services include regulatory support and project management to assist our partners in obtaining and maintaining regulatory approvals.

Supply chain services

Skyepharma provides integrated supply chain services adapted to the needs of each partner: from the purchase of APIs and excipients to manufacturing, packaging, warehousing and shipping to delivery locations, all around the world.

Skyepharma provides value across the whole supply chain by ensuring:

- Logistics and supply chain management handled by dedicated teams of experts in logistics and export
- Single point of contact through a committed project manager
- Fast evaluation process in terms of industrial execution
- Strong operational excellence program
- Extensive experience in contract development and manufacturing activities for third parties
- Location and material status computerized
- Compliant with USP* requirement for “controlled temperature”



WAREHOUSING OFFER

- 4’320 pallet spaces in cGMP, controlled and monitored warehouse

Regulatory services

Skyepharma assists its clients in preparing their submissions, for product maintenance processes and advises on regulatory strategies, such as for:

- NDA, ANDA and EU-Marketing Authorization Application writing
- Supplement and variation writing and other lifecycle management activities
- Answers to health authorities’ inquiries and periodic registrations
- Proactive regulatory intelligence monitoring

Skyepharma regulatory affairs department is experienced in assisting on projects for all kind of products (health/dietary), markets and specificities.

CERTIFICATIONS

The facility is EU GMP certified and FDA registered for development and manufacturing with extensive experience in US and EU regulatory filings in collaboration with pharmaceutical companies of all sizes.

We have a constant track-record of passing inspections, with no major nor critical issue observed:

- FDA approved since 1998
- Anvisa approved since 2013
- Registered at South Korean MFDS since 2013
- EU GMP certified facility

Skyepharma facility has a consistent history of regulatory approvals for development, manufacturing and packaging of pharmaceutical products for European, North and South American and Asian markets.

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