KYMOS
GROUP

Company Presentation

2024

01
Company Overview

KYMOS GROUP

KYMOS GROUP
Ronda Can Fatjó 5D
08290 Cerdanyola del Vallès
Barcelona (Spain) | www.kymos.com

Our Name

The word KYMOS is inspired by the etymology of the word chemistry, which derivates from the Latin word alchimia, coming from the Arabic word al-khemia (fusion), the Greek word khemia (transformation), and the ancient Egyptian word kéme (soil, origin of life).

Transformation, change and evolution are our inspiration

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Company Overview - Services

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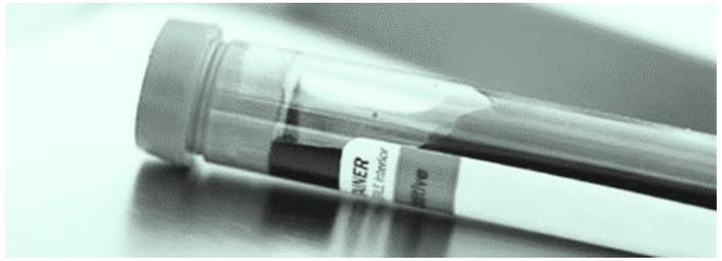
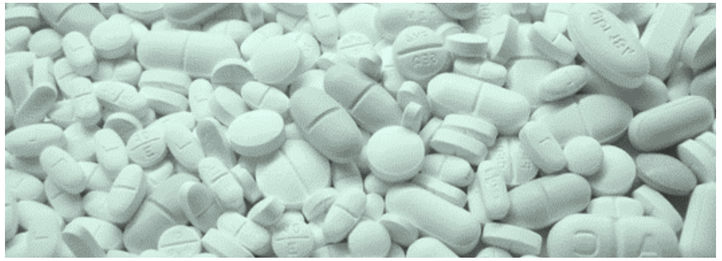
Our Value Proposition

KYMOS is a company devoted to provide analytical expertise and testing capabilities to third parties for research, development, and quality control of biopharmaceuticals.

Bioanalysis
(preclinical & clinical studies)



CMC Analysis
(chemistry, manufacturing & control)



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Our Value Proposition

	Small molecules	Biologics	Advanced therapies
Bioanalysis (preclinical & clinical studies)	Mass Spectrometry Bioequivalence studies	PK & ADA testing Cell Based Assays Enzyme activity	Viral vector DNA & RNA biodistribution & TK/PK Nucleic Acids qPCR
	Full Preclinical Studies Package Pharmacokinetics calculations and reports		
CMC Analysis (chemistry, manufacturing & control)	Stability Studies Microbiology Batch Testing Importation & Batch Release		
	Analytical Development Raw materials analysis Chemical Impurities Extractables & Leachables	AMT of biosimilars Characterization Potency assays	Characterization of carrier (virus, LNP) & transgene Potency assay: infectivity & expression
		Biopharmaceutical Impurities	

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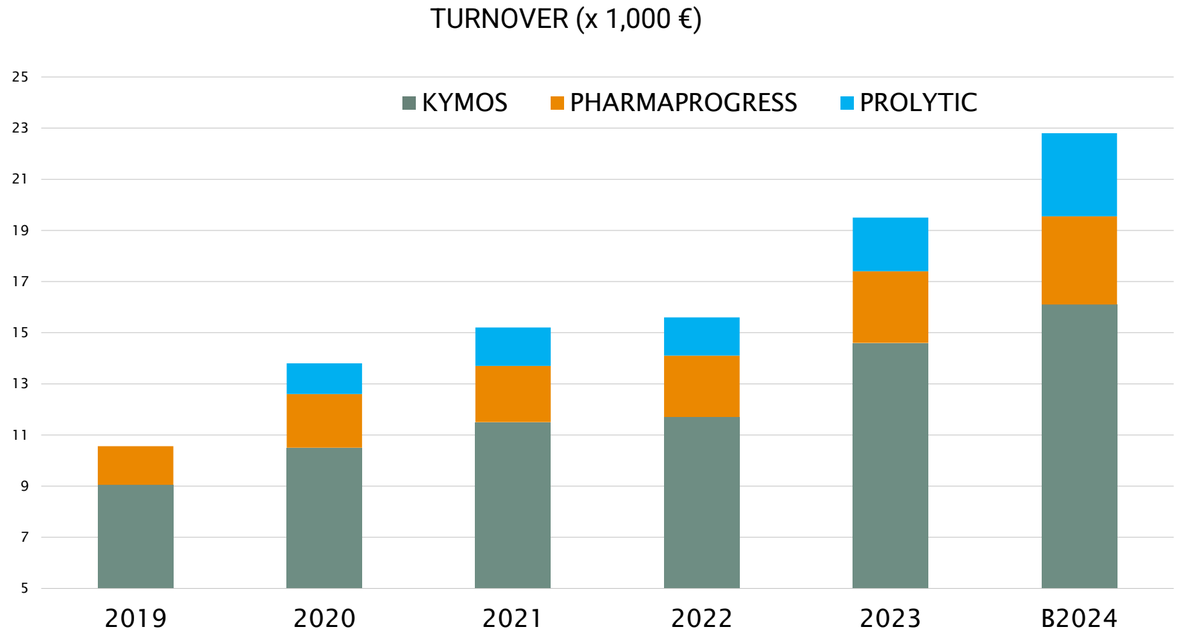
Fast growing European CRO
(contract research organization)

reliable and experienced management team & solid financial structure



Shareholders:

- Founder and key managers
- Family Office from pharma sector

Governance:

- CEO, CFO and General Site Managers
- Steering Committee
- Board of Directors of 6 members with quarterly meeting
- External members in the Board (2)

Compliance:

- Audited Group (Grand Thorton)
- Corporate Social Responsibility
- Code of Conduct
- Equality Plan
- Environmental & Safety
- Privacy & Confidentiality
- Quality certifications

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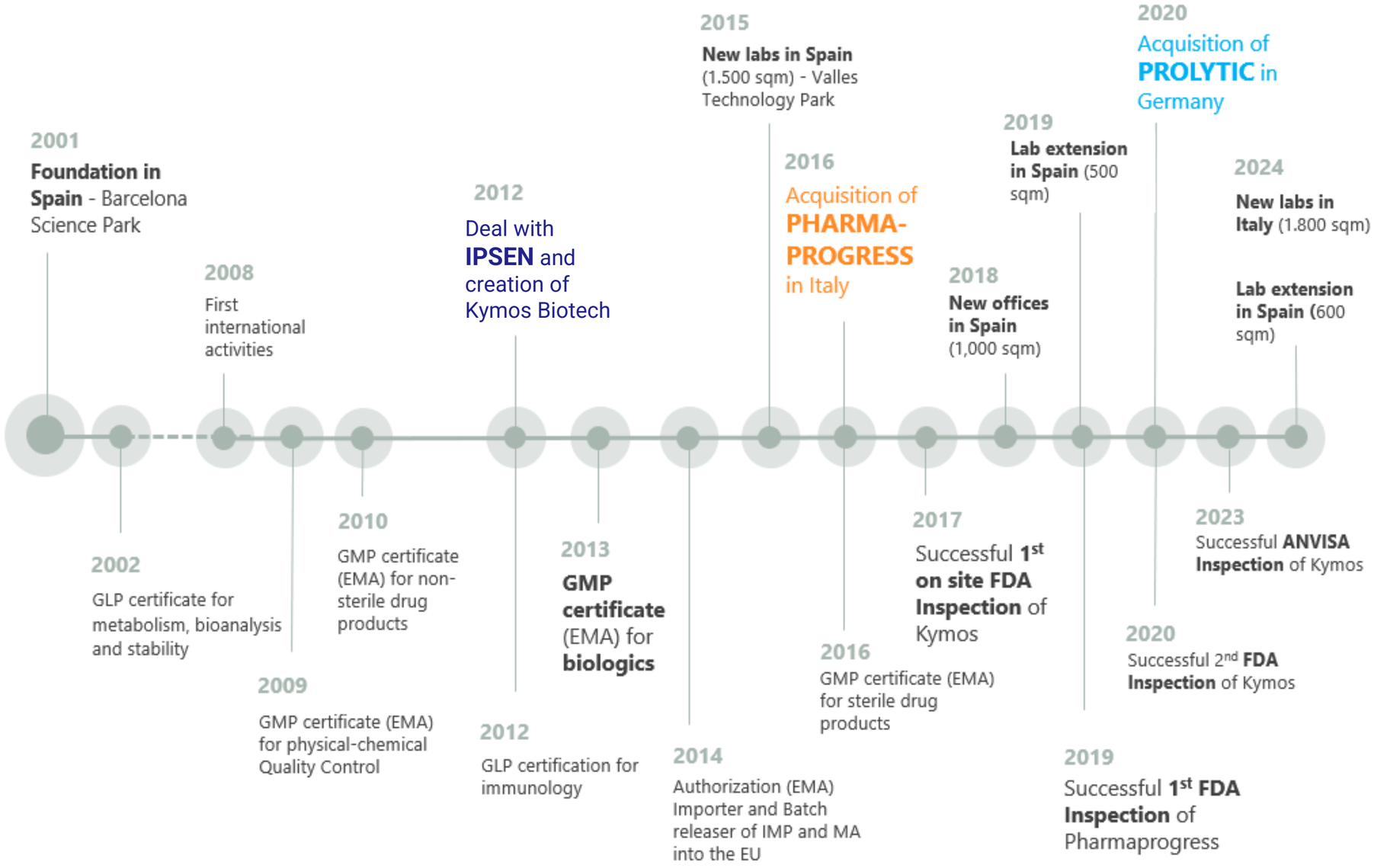

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Company Overview - Markets

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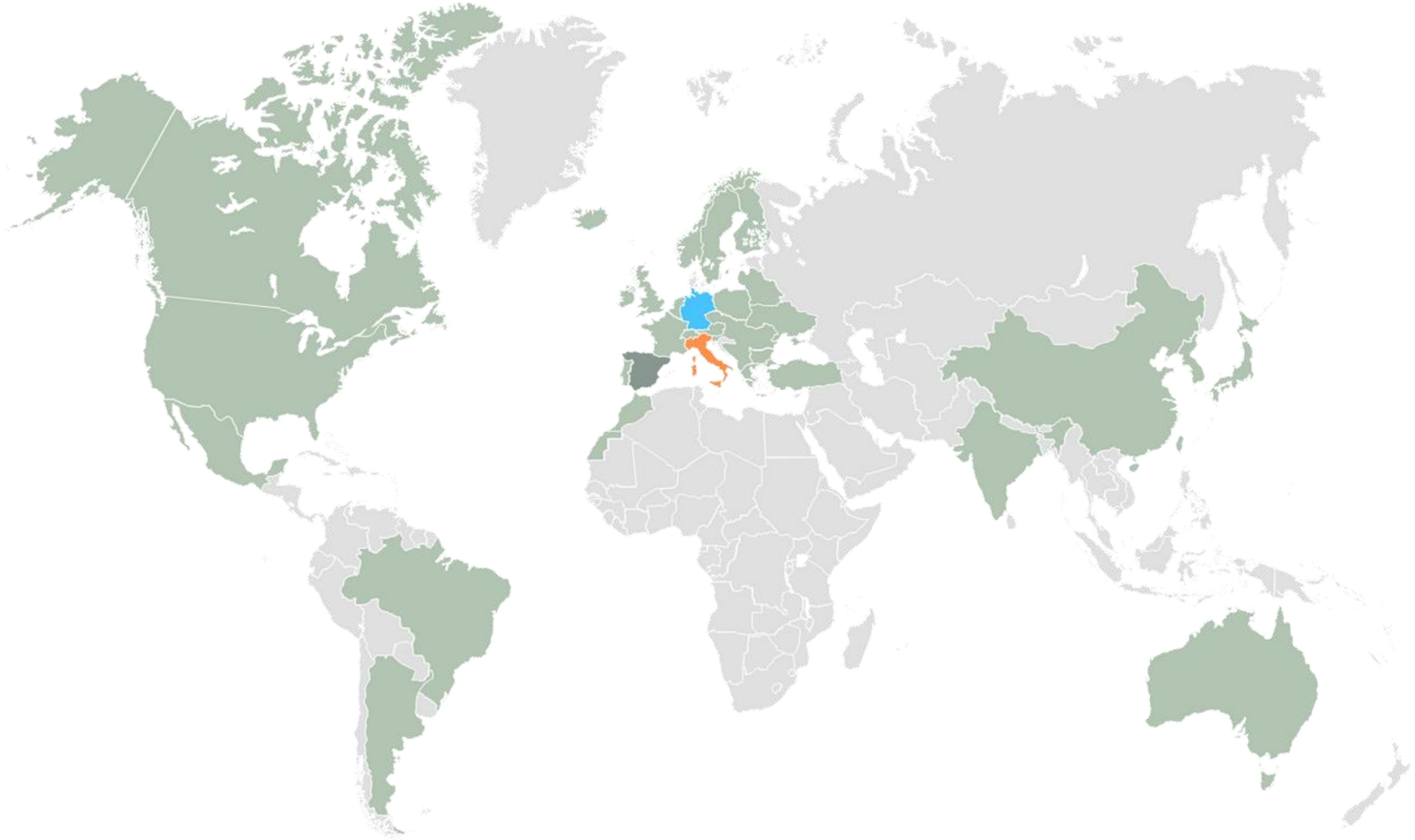
Global presence

European based group with headquarters in Barcelona, laboratories in Barcelona (ES), Ancona (IT) and Frankfurt (DE), commercial offices in Paris (FR) and Milan (IT), a branch in Seoul (KR) and clients of >60 countries, being Asia the fastest growing area.



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Company Overview - Clients

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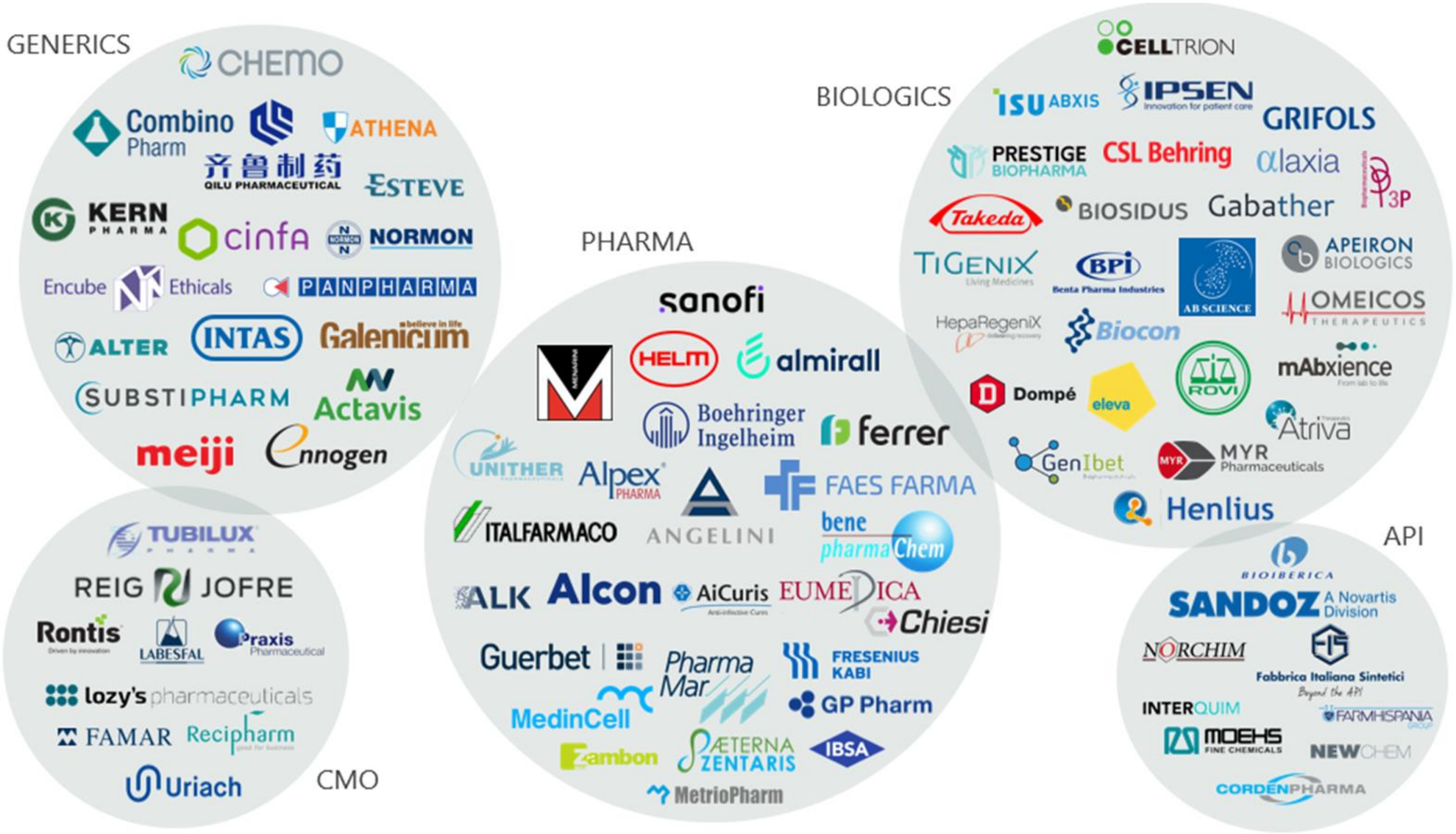

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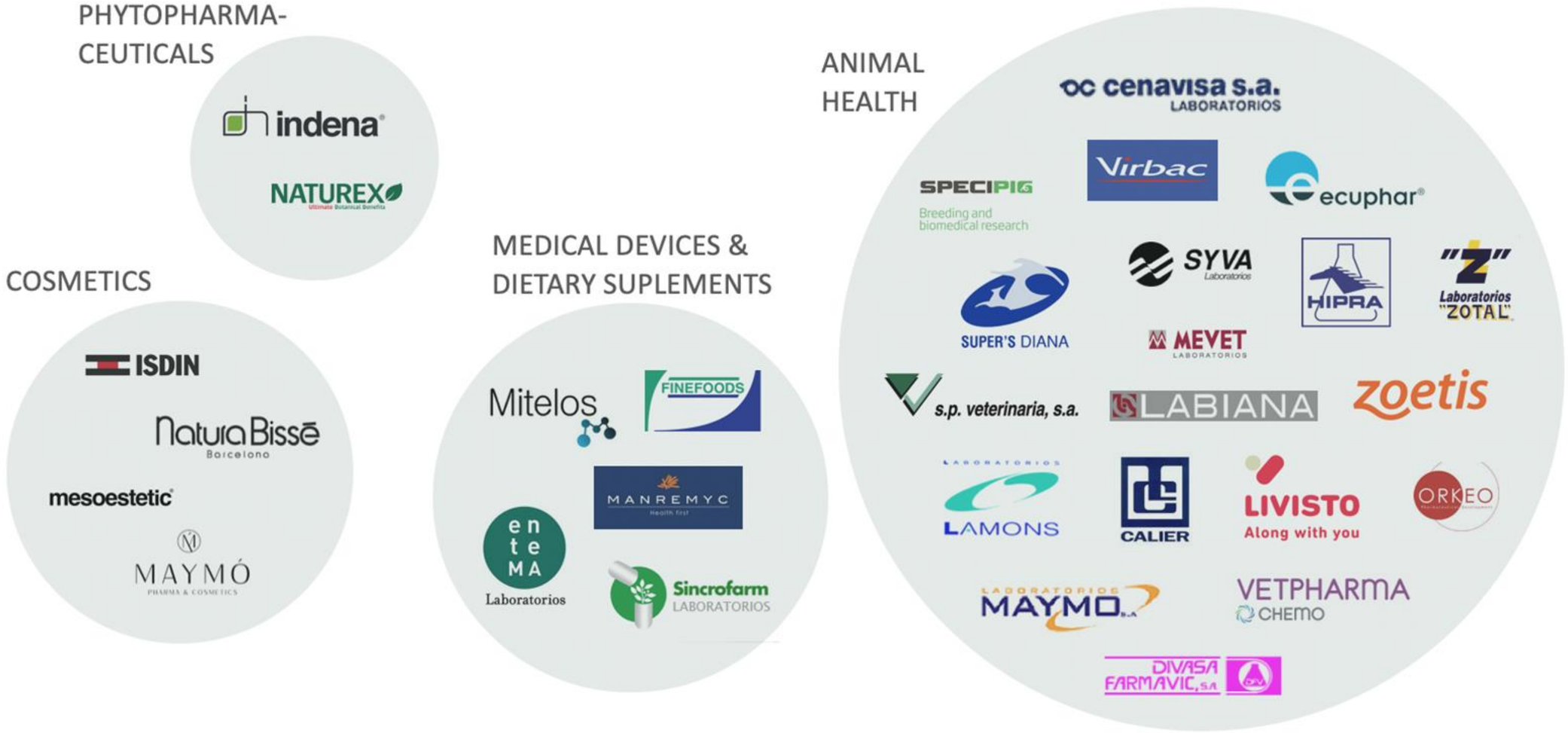

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Company Overview - Partners

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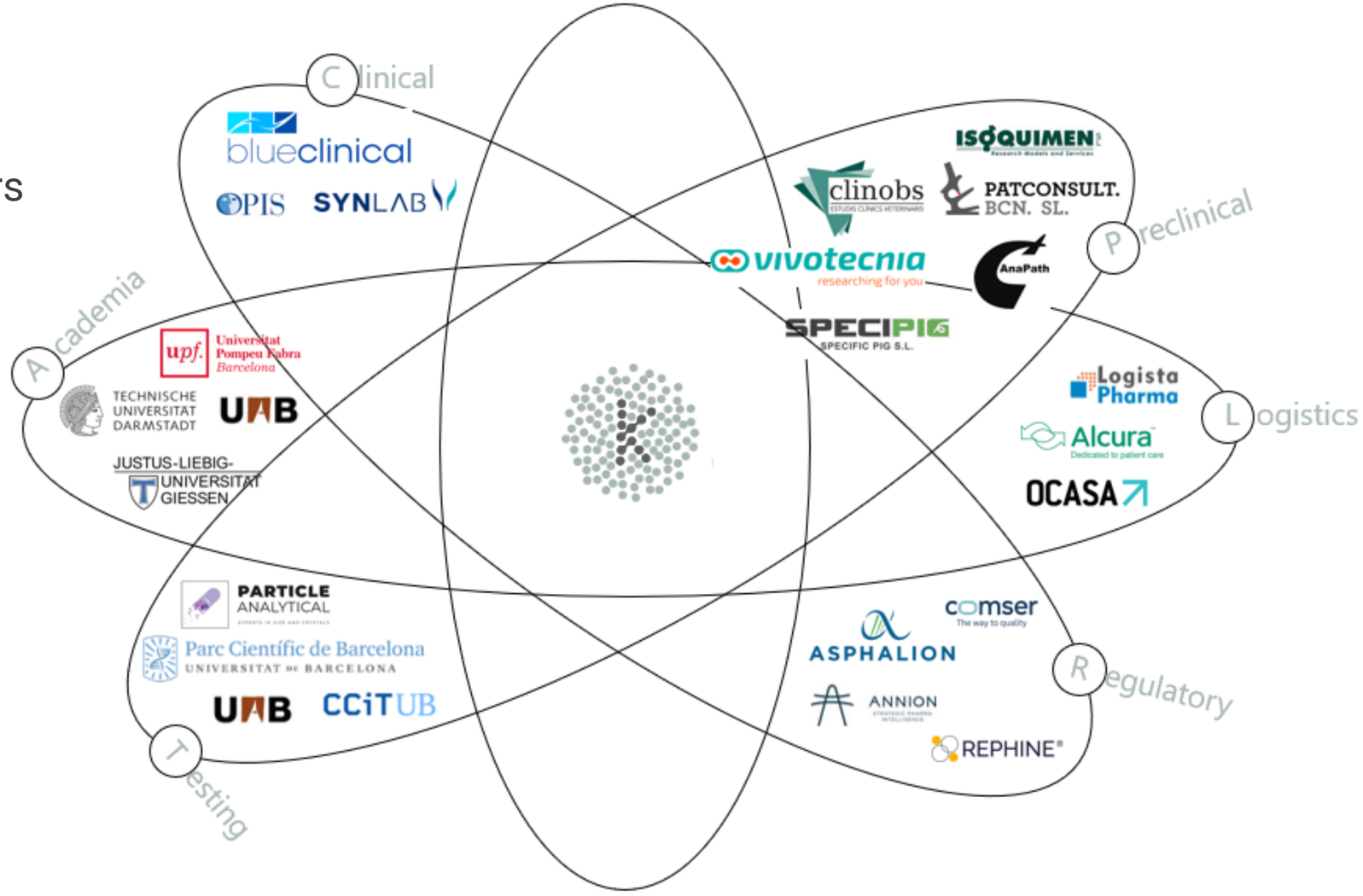
One-stop-shop provider with reliable and certified partners



02
Premises & Equipment

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Premises & Equipment

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Barcelona, Spain

Building 1 - Offices (1,200 sqm)
Building 2 - Laboratories (1,800 sqm)
Building 3 – Laboratories (600 sqm)
Staff of 130 people

- Fit to purpose building: technical gas station, emergency electric supply, purified water plant, and IT data room
- GMP and GLP certified, EMA and FDA inspected
- 5 laboratories: Bioanalysis, Immunology, Physical-Chemical, Microbiology, Biopharma testing.
- Sample storage, climatic chambers and freezers
- Containment room for high potency products (HAPI) up to OEL4 and BSL2 labs.

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Ancona, Italy

Brand new laboratories (1,800 sqm)
Staff of 30 people

- New facilities (2023)
- GMP certified, EMA and FDA inspected
- 3 laboratories: Analytical Development, Impurities testing & OINDP testing
- Complementary capabilities in LC-MS/MS and GC/MS analysis.
- Experience in extractables & leachables, impurities identification and nitrosamines.
- Instrumentation and know-how for OINDP testing.

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Frankfurt, Germany

Laboratories (1,000 sqm)
Staff of 25 people

- Recently fully renovated facilities
- GLP certified and GCP compliant
- 3 labs: Small Molecules, Immunological Test Systems, Nucleic Acids
- LC-MS/MS / ELISA / qPCR
- Small Molecules (LC-MS/MS)
- Immunological test Systems (ELISA)
- Nucleic Acids (qPCR)
- Enzyme Activity
- Pharmacokinetic Evaluation

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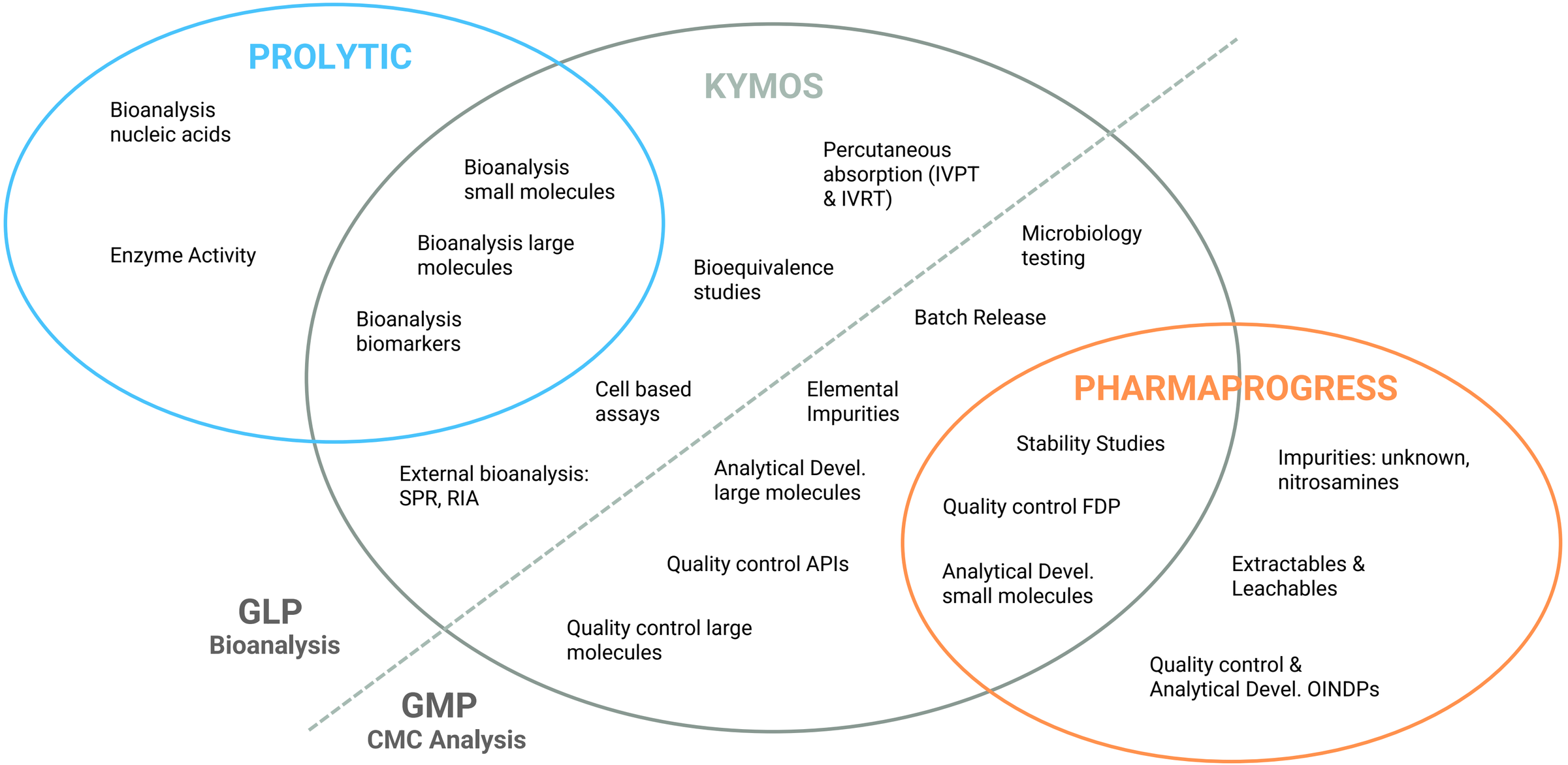

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Instruments at Kymos Group (GMP & GLP compliant)

Immunology

- WIZARD gamma counter for RIA assays
- SpectraMax M3/M5 microplate ELISA reader (2)
- Biotek Epoch / Synergy microplate ELISA reader (2)
- MESO QuickPlex SQ 120 Meso Scale Discovery for ECLA
- Guava easyCyte flow cytometer for cell assays
- Pharmacia PhastSystem high speed electrophoresis
- Multhiphore II electrophoresis system GE (2)
- GS-900 calibrated densitometer for electrophoresis
- Agilent 2100 Bioanalyzer chip electrophoresis
- Solo VPE UV-visible spectrophotometer
- Agilent capillary electrophoresis with LIF detection
- Beckman PA800S Plus capillary electrophoresis (2)
- Protein Simple Image isoelectric focusing iCE3
- QuantStudio 7 Flex real time qPCR (2)
- King Fisher Flex benchtop sample prep. Instrument (2)
- Cell laboratory fully equipped (2)

Chromatography & analizers

- HPLC Alliance Waters and Agilent 1100, 1200, 1260, and Arc (45 units) coupled to UV diode array, fluorescence, refraction index, electrochemical, amperometry, light scattering, CAD and mass detector QDa.
- Ionic Chromatography
- UHPLC (10): Agilent 1290 and Waters Acquity
- Agilent Gas chromatography (6) coupled to head-space injection system, with FID/ECD detection
- Agilent atomic absorption spectrometer
- Mercury analyzer DMA-80 Milestone
- UV-visible spectrophotometer (diode array)
- FTIR Cary 630 Agilent

Mass spectrometry

- LC-MS/MS SCIEX API 3.200 (1), 4.000 (8), 5.500 Qtrap (4), 6.500 Plus (3) and 6.500 Plus QTRAP (1) and LC-MS/MS TQS Waters
- Qtof Xevo G2-S Waters with BiopharmaLynx and MaxEnt mass spectrometer
- ICP/MS Agilent 7.700 and 7.800 (2) and digestion system Milestone Ultrawave (2)
- LC-MS/MS Infinity with MS 6491 Agilent (2)
- GC-MS Agilent (2)
- Orbitrap Exploris™ 120 Mass Spectrometer

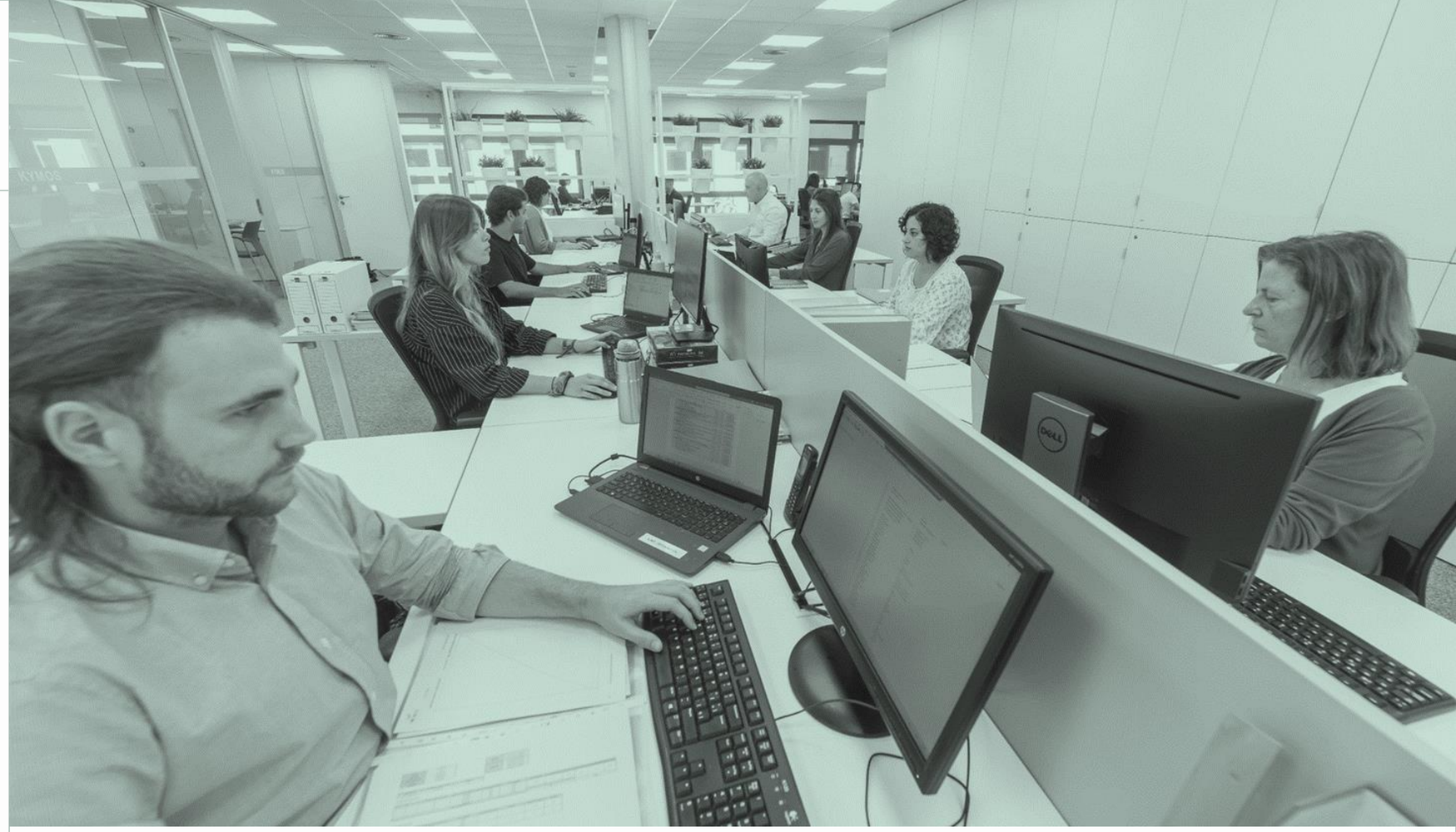
Other instruments

- Franz cells Crown Glass V-Series manual (1 instruments, 9 cells)
- Franz cells Phoenix RDS automatic (2 instruments, 12 cells each)
- Climatic chambers for ICH stability studies and photostability chamber
- Dissolution test (8), disintegrating test and friability test
- Particle Size Distribution Malvern Mastersizer 3000
- TGA & DSC Mettler Toledo
- Cascade impactor for OINDP (Andersen and NGI)
- Viscosimeter, polarimeter, Karl Fischer (volumetric and coulometric), melting point, osmometer (2)
- Subvisible particles Pamas (2)
- TOC analyzer
- Microbiology laboratory fully equipped
- Isolator (for sterility testing)
- Gliding force and Autoinjector Functionality testing (Zwick Roell)

Instruments at University (GLP compliant)

- Maldi TOF
- NMR systems
- SPR (Biacore T200)
- Circular Dicroism
- Protein sequencer (Edman degradation)

03
Quality & Organization



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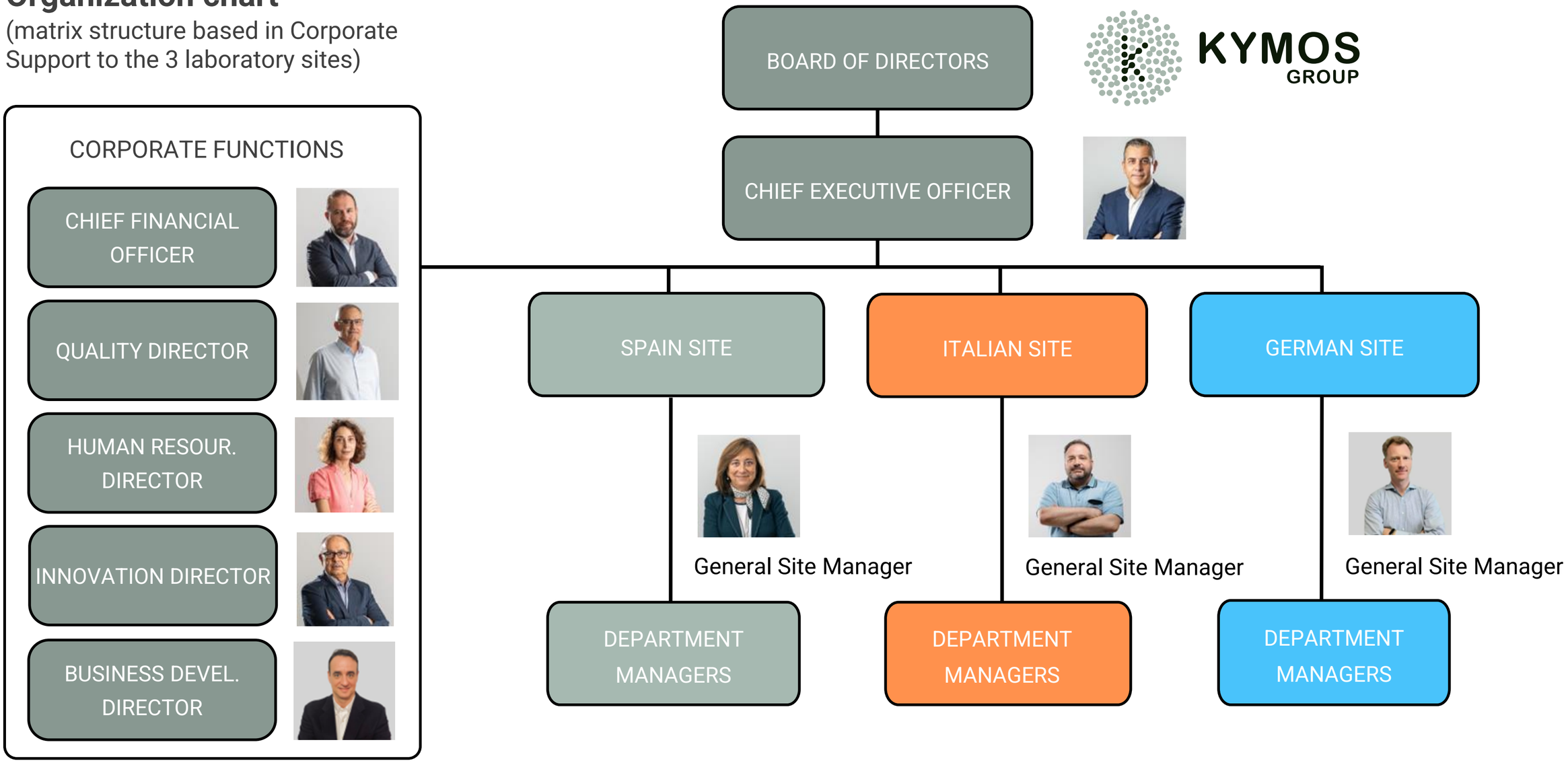
Organization chart

(matrix structure based in Corporate Support to the 3 laboratory sites)



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Quality System

Unified Quality System for GMP, GLP, GCP and GXP-like activities

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

agencia española de medicamentos y productos sanitarios

Agenzia Italiana del Farmaco
AIFA

HESSEN

ANVISA

FDA
The Food and Drug Administration

Corporate

- Corporate structure to support the Sites Managers
- Central Quality Assurance function with staff in each site
- Crossed self-inspections between sites
- Computerized systems under validation (21 CFR part 11, EU GMP Annex 11)
- LIMS Labware and Empower 3
- Data Integrity compliance (EMA, FDA, MHRA, ISPE guides).

Spain Site

- GMP certification: quality control for small molecules and biologics
- GLP certification
- GCP compliance
- EMA (AEMPS) and FDA successfully inspected
- ANVISA certification for bioequivalence studies
- 4 Qualified Persons responsible for batch testing & release
- Computer System Validation function
- CIR (Crédit Impôt Recherche)

Italy Site

- GMP certification for small molecules
- EMA (AIFA) and FDA successfully inspected
- 2 Qualified Persons for batch testing

Germany Site

- GLP certification for analytical studies on biological material and Physical-chemical properties and determination of content
- Successfully inspected by German authorities
- CIR (Crédit Impôt Recherche)
- Quality Assurance person

04
Services

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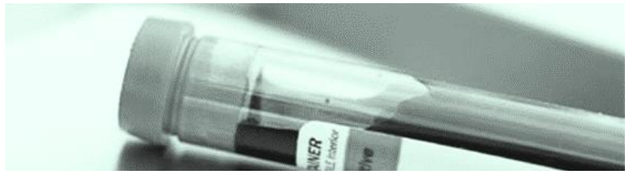
Bioanalysis

(preclinical & clinical studies)



- Full preclinical study management
- Full bioequivalence studies
- PK of small molecules by LC-MS/MS, HRMS, and ICP-MS
- Residue depletion studies (animal health)
- Invitro release & percutaneous release
- PK studies of biologics by ELISA, ECLA, RIA
- ADA testing in immunogenicity studies
- Biomarkers determination by ECLA multiplex and LUMINEX
- Binding assays by SPR
- Glycans by capillary electrophoresis
- Enzyme activity
- Nucleic acids analysis by qCPR
- Nucleic acids bioanalysis by Hybridization ELISA & MS Spectrometry
- Cell-based assays for neutralizing antibodies
- Histological preparation
- Pathology evaluation

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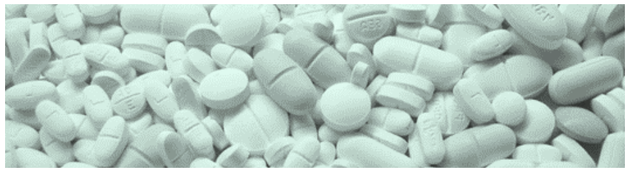
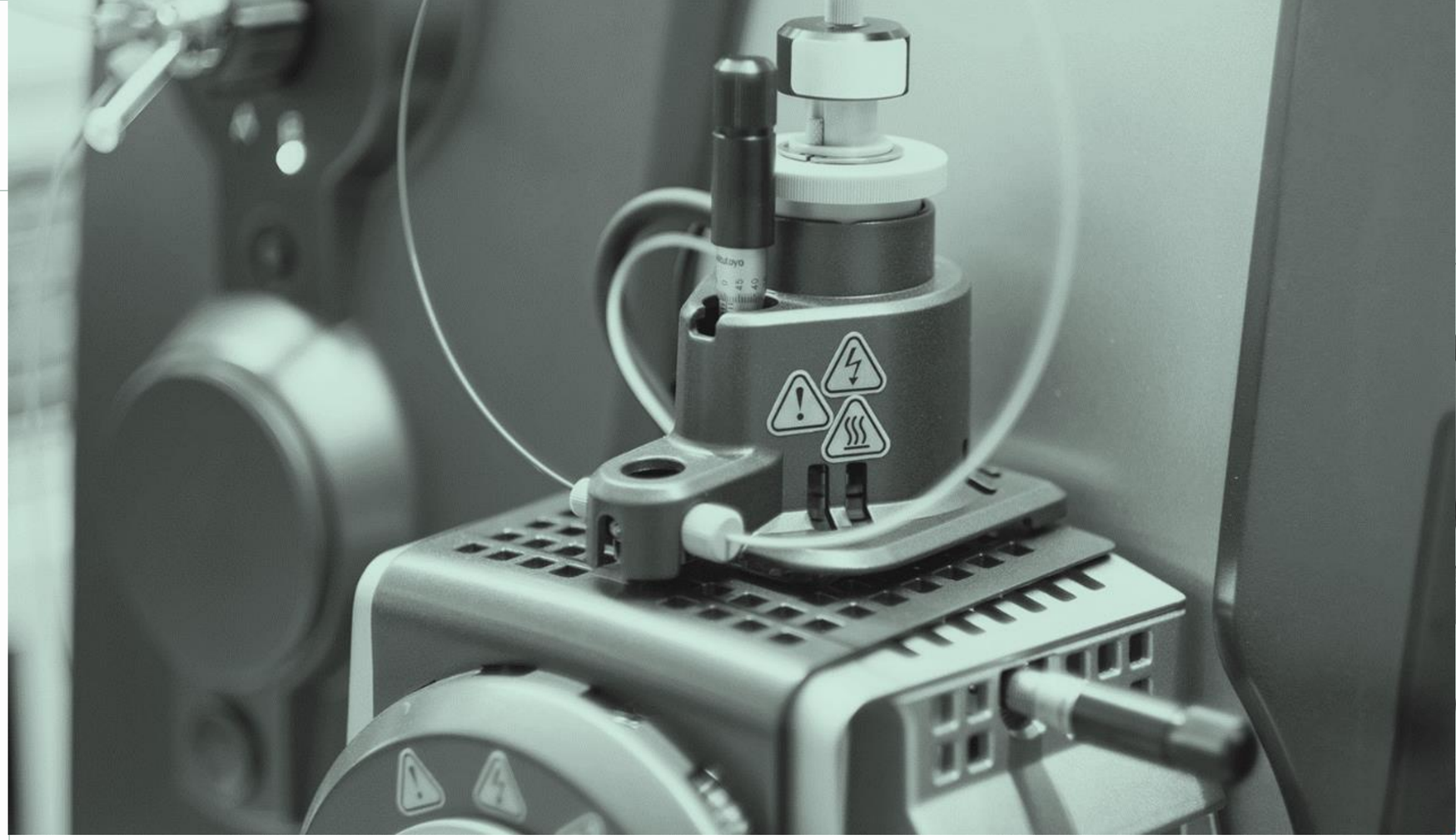
CMC Analytical

(chemistry, manufacturing & control)



- Raw material testing (compendial and non-compendia methods)
- Method validation for assay, related substances, residual solvents by LC & GC
- Physical determinations (pH, melting point, density, osmolarity, particle, dissolution)
- Orally Inhaled & Nasal Drug Product testing
- Elemental impurities, Nitrosamines and Extractables & Leachables
- Stability studies and sample storage (ICH, on-going, photostability, in-use, holding time)
- Microbiology for sterile and non-sterile products and endotoxines
- Characterization and comparability of biologics and biosimilars
- Building blocks of glycans and antifactor testing in heparines
- Cell based potency assays for QC
- Quality control of biologics and biosimilars
- Viral vector characterization and quality control
- Batch release into the European Union

05
Bioanalysis small mol.



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Bioanalysis small molecules

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Bioanalysis of small molecules

peptides
innovative drugs
metal-containing drugs
generic drugs
biomarkers

ICH harmonisation for better health
ICH M10 Compliant

Services provided:

- Development and validation of bioanalytical methods by LC-MS/MS and ICP-MS and High-Resolution MS (QTof)
- Quantification of drug levels in preclinical and clinical samples (studies from phase I to IV)
- PK calculations, data analysis & reporting (WinNonlin)

Type of studies:

- GLP-like methods in early development
- Preclinical studies
- Pharmacokinetics & pharmacodynamic calculations & statistics
- Metabolite identification and quantitation
- Clinical studies
- Phase I-IV pharmacokinetics, First-in-Man & Dose searching
- Drug-drug interaction studies
- Bioequivalence studies
- In vitro percutaneous absorption
- Food and drug interaction studies
- Preclinical and animal health studies
- Histopathology

Bioanalysis small molecules

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Full Bioequivalence studies

full study management
clinical phase, monitoring and bioanalysis

Preparatory and support activities:

- Dissolution profiles in different media and stability complementary data, if required by the IMPD
- Review of IMPD and obtention of Eudra-CT number
- Quality Control and Release of Clinical batches
- Design of study (number of volunteers, time points, fast and feed,…)
- Validation of non-proprietary bioanalytical methods (cost-free). See the list of validated methods
- Submission to the Ethical Committee and Medicines Agency

Management of the clinical phase:

- Coordination of phase I center: certified & audited EU partners
- DP procurement, labelling, storage and supply
- Study monitoring
- Pharmacokinetic and Clinical report writing

Bioanalysis and pharmacokinetics:

- Sample collection and shipment
- Bioanalysis of samples
- Pharmacokinetic and Statistic data analysis (WinNonlin®)

Bioanalysis small molecules

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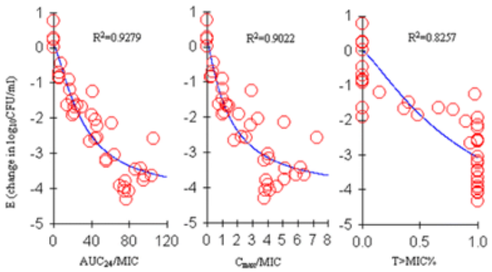
Pharmacokinetics

Phoenix WinNonLin
Version 8.2 validated

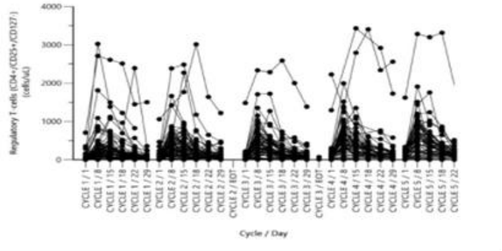


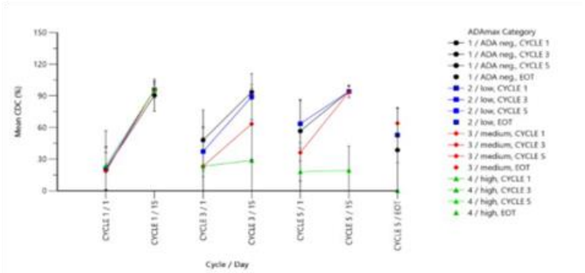
Services provided:

- Phoenix WinNonlin® software 8.2 gold standard
- Pharmacokinetic/pharmacodynamic and toxicokinetic modeling
- Multi-matrix analyses (plasma, serum, urine, blood...), dosing schedules and dosing routes using NCA
- Bioequivalence evaluation of averages, individuals, populations

Type of studies:

- Non-compartmental analysis (NCA)
- Compartmental built-in and self-generated modelling
- Bioequivalence (AUC, Tmax, Cmax)
- Preclinical and clinical evaluations in human and animal health
- Compartmental evaluation and special considerations





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Percutaneous absorption

Bioequivalence of topical products

“In-vitro” Release Test (IVRT)

Using Franz Cells instrument and artificial membranes for characterization of topical formulations according to EMA draft guideline (GMP)

- Optimization of different formulations
- Development and validation of release rate method for topical formulations.
- Quality control for in vitro release of batches.

“In-vitro” Permeation Test (IVPT)

Bioequivalence of topical drug products by determination of percutaneous absorption with skin samples in accordance with EMA draft guideline (GLP), avoiding clinical end-point studies.

- Optimization and comparison of formulations.
- Selection of suitable excipients.
- Selection of lead candidate formulations for topical products.
- Skin stripping and layering to measure skin penetration
- Assessment of safety of cosmetic actives
- Absorption studies through nails, mucosa or cornea.

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Preclinical and animal health studies

Multicentric studies with strategic partners

Type of studies:

- Preclinical studies of drug products for human use
- Clinical studies of drug products for veterinary use
- Residue depletion in edibles of animals treated with veterinary DPs
- Bioequivalence studies in plasma
- Immunological studies for biologics

Services provided:

- Development and validation of bioanalytical methods in animal matrices
- Quantification of drug levels in preclinical and clinical samples
- Toxicokinetics, PK, PD, bioavailability, data analysis & reporting
- Residue depletion in milk, eggs, honey, point of injection and tissues
- Histopathology services
- Long list of **validated methods** for generics

Study management & facilities:

- Study Design under GLP compliance
- Regulatory support, Animal welfare and Ethical Committee management
- Blood, plasma and complex matrices such as liver, fat, muscle or brain
- Multiple animal models: rats, mice, rabbits, ferrets, minipigs, pigs, cats, dogs, non-human primates, swine, cattle, sheep, poultry and horses

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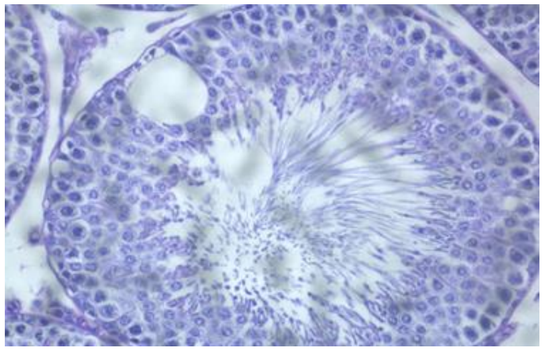
PATCONSULT. LAB. SL.

Investee company of Kymos®

Histopathology services

GLP-certified
30 years of experience in toxicological pathology
Histopathology evaluation and consultancy



Histotechnique

- Histological preparation of 50.000 - 70.000 organs/tissues per year
- Histological processing of samples from all species used in Experimental Pathology
- Organ trimming according to RITA recommendations for GLP toxicity studies in rat
- Slide scanning (Hamamatsu Digital Slide Scanner)

Histopathology, histomorphometry and image analysis

- GLP preclinical regulatory studies (toxicologic pathology)
- Experimental pathology (efficacy assays, experimental models)
- Medical device studies (biocompatibility, tolerance studies, subcutis, muscle, bone implants).
- Histopathological data management software (PathData System)

Additional services

- Consultancy services for the design of preclinical/experimental pathology studies and specific histopathological problems.
- Worldwide network of histopathology partners.

06
Bioanalysis biologics

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Bioanalysis biologics

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Bioanalysis of biologics

peptides
glyco & phosphoproteins
biomarkers
hormones
enzymes
biosimilars
mAb
ADC
oligonucleotides
toxins

ICH harmonisation for better health
ICH M10 Compliant

Bioanalytical services

Services provided:

- Method development from scratch or method transfer
- Quantification of drug levels in preclinical and clinical samples (from phase I to IV)
- Immunoassays and Neutralization assays
- Pharmacokinetics calculations
- Method validation, stability and cross-validation
- Obtainment of polyclonal antibodies for assays (in rabbits)
- UV-Vis enzyme activity quantification
- Bioanalysis of nucleic acids

Analytical platforms available

- Immunoassays:
  - ELISA: direct, sandwich, bridge, competitive using different detection techniques (colorimetric, fluorescence, time resolved fluorescence, luminescence)
  - ECLA: electrochemiluminescence by MesoScale Discovery
- HPLC-MS/MS: tryptic digestion of the protein and quantification of characteristic (signature) peptides
- Real Time qPCR (RTqPCR), LC-MS/MS and Hybridization ELISA

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Bioanalysis biologics

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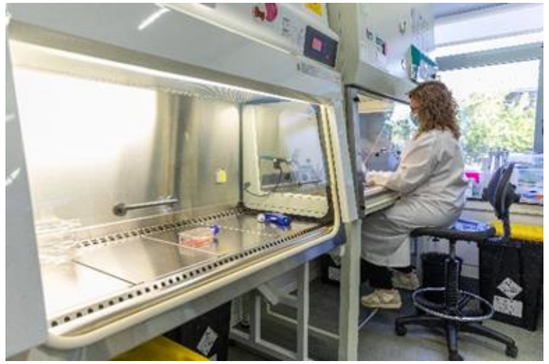
Bioanalysis of biologics

peptides
glyco & phosphoproteins
biomarkers
hormones
enzymes
biosimilars
mAb
ADC
oligonucleotides
toxins



Immunogenicity

Services provided:

- Determination of binding Anti-Drug Antibodies (ADA) against peptides, proteins or antibodies
  - Screening assays for detection of positive samples
  - Confirmatory assays for ruling out false positive results
  - Isotyping assays to determine the ADA isotypes
  - Titration assays to quantify the immune response
- Neutralizing assays to assess ADA drug function inhibition using several alternative approaches:
  - Cell-based assays (CBA)
  - Binding assays using ELISA, ECLA or SPR

Analytical platforms available

- Immunoassays: ELISA, ECLA
- Surface Plasmon Resonance (SPR) (Biacore®)

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Bioanalysis biologics

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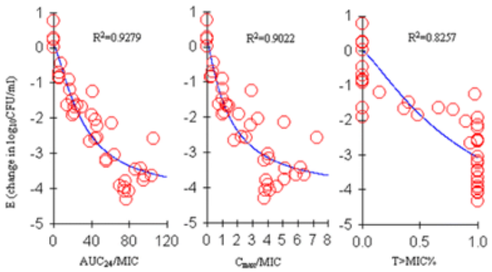
Pharmacokinetics

Phoenix WinNonLin
Version 8.2 validated

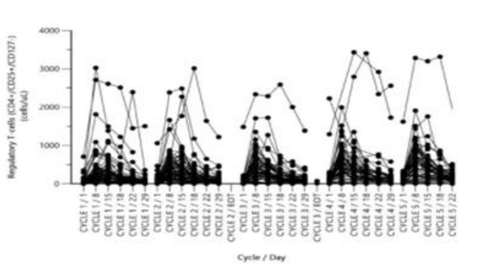


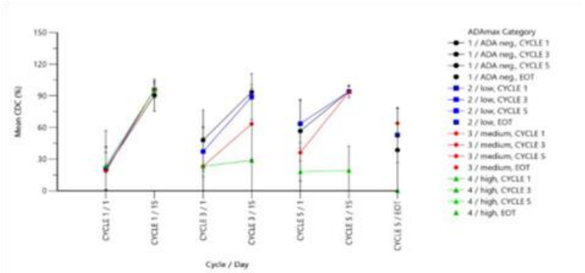
Services provided:

- Phoenix WinNonlin® software 8.2 gold standard
- Pharmacokinetic/pharmacodynamic and toxicokinetic modeling
- Multi-matrix analyses (plasma, serum, urine, blood...), dosing schedules and dosing routes using NCA
- Bioequivalence evaluation of averages, individuals, populations

Type of studies:

- Non-compartmental analysis (NCA)
- Compartmental built-in and self-generated modelling
- Bioequivalence (AUC, Tmax, Cmax)
- Preclinical and clinical evaluations in human and animal health
- Compartmental evaluation and special considerations





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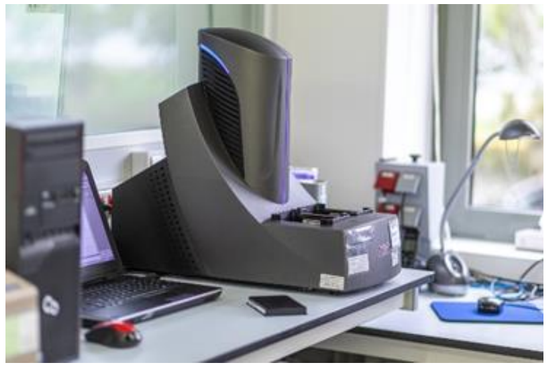
Biomarkers

MSD® and Luminex® for proteins: cytokines, hormones, growth factors, etc.

qPCR, ELISA and LC-MS/MS for genetic biomarkers: RNA, mRNA, miRNA, etc.

LC-MS/MS for small molecule biomarkers



Services provided:

- Validation “fit-to purpose” methods for biomarkers using commercially available kits.
- Prevalidated panels available – Ready to use
- Exploratory screenings for use an endpoint in future clinical trials
- Development of methods from scratch
- Customized multiplexing panels
- Pharmacodynamic studies for drug efficacy and safety
- Species: human, mouse, non-human primate, rat, canine, chicken, pig and others
- Matrices: plasma, serum, CSF, cell culture supernatant, cell homogenates, urine, saliva and others

Therapeutic areas (Multiplex Protein Panels):

INFLAMMATORY BIOMARKERS	NEUROLOGY BIOMARKERS
- Inflammatory panels – Cytokine and Chemokine panels	- Neurology and Neuroinflammation panels
ONCOLOGY BIOMARKERS	**VASCULAR AND ANGIOGENESIS BIOMARKERS**
- Oncology panels	- Vascular and Angiogenesis panels
CARDIOLOGY BIOMARKERS	**SYSTEMIC DISEASE BIOMARKERS**
- Cardiovascular and Cardiac Injury panels	- Kidney Injury Panels - Metabolic panels

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Enzyme activity

natural enzymes
therapeutic enzymes
enzymatic biomarkers
enzyme inhibitor DPs

UV-Vis reader for absorption, luminescence & fluorescence detection

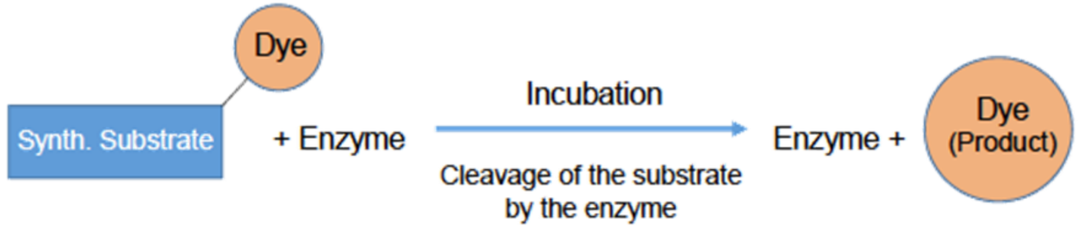
Determination of enzyme activity

Biocatalytic activity quantification:

- Endpoint measurements: Calibration curve based on amount of substrate consumed after a defined time period
- Real-time kinetics: Specific and volume activity per time unit

Type of studies:

- Kinetic measurements of enzyme activity
- Enzyme/substrate specificity analysis
- Inhibitor efficacy and inhibition reversibility screenings
- Applications in biological samples and in formulation samples



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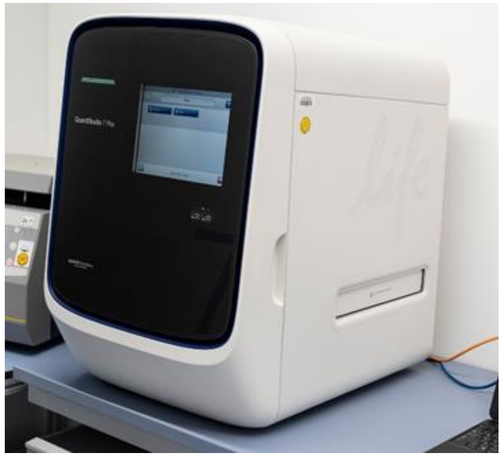
Nucleic acid bioanalysis

DNA, mRNA, microRNA, siRNA, RNA-based vaccines, aptamers, antagomiRs



Bioanalysis of Nucleic Acids (DNA & RNA)

Services provided:

- Quantification of biomarkers by Real Time qPCR (RTqPCR)
- Quantification of therapeutic oligonucleotides by hybridization ELISA
- Automated magnetic bead isolation and purification
- Following FDA, EMA, MHLW, MAFF and METI guidelines

Real Time qPCR for biomarkers:

- Ultra-sensitive qPCR detection up to 1pg/ml
- Quantification of DNA, mRNA, siRNA, aptamers, antagomiRs
- ΔΔCt gene expression in biological matrices
- Detection of viral and bacterial RNA/DNA
- Biodistribution of DNA/RNA-based DPs or vaccines
- Allograft decellularization efficiency by residual human DNA analysis
- Quantification of host-related residual DNA/RNA (E. Coli, CHO, etc.)
- Mycoplasma qPCR assays in cell culture, media and biologics

Hybridization ELISA for therapeutic oligonucleotides:

- ELISA-based detection in the range 0.5–1.000 ng/ml
- Substance and DP quantification in formulation & biological matrices

07
CMC small mol.

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CMC small molecules

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CMC of small molecules

active ingredients
human & veterinary DPs
excipients
intermediates
IMPs and generics

Analytical Development and Validation

- Method Transfer and optimization
- Stress Testing
- Method Development and Validation for:
  - Quality Control
  - Stability indicating methods
- Cleaning validation (APIs & detergent contaminants)
- Environmental testing (reused solvents and water waste)

Quality Control of raw materials and drug products

- Compendial methods
- Proprietary methods
- OOS and investigation management
- Data management with LIMS system with audit trail and data integrity (21 CFR part 11 compliance)

Stability Studies

- Full management of stability programs
- Sample storage
- ICH stability studies
- On going stability studies

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CMC of small molecules

active ingredients
human & veterinary DPs
excipients
intermediates
IMPs and generics

Quality control of small molecules

- General Identification Tests (IR, TLC, HPLC)
- Assay (UV/Vis, IR, AAS, titration, HPLC, UPLC, GC, LC-MS) and dosage uniformity
- Related substances identification (GC, HPLC, GC/MS, LC/MS)
- Physical tests: pH, viscosity, density, polarimetry, refraction index, melting point, osmolality, appearance.
- Moisture (Karl Fisher, loss on drying)
- Limit tests (heavy metals, ash, anions)
- Residual solvents (volatile organic compounds & impurities)
- Impurities identification (HPLC, LC-MS)
- Elemental impurities (AAS, ICP-MS)
- Nitrosamine impurities (LC-MS-MS, HS-GC-MS)
- Formulations tests: disintegration, dissolution test, hardness, friability.
- Dissolution profiles: type I, II and IV (flow through cell) and enhanced cells
- Semi-solids in vitro release testing (vertical diffusion cells)
- Particulate matter (visible and subvisible particles)
- Particle size distribution (Malvern Mastersizer 3000)
- Extractables & Leachables
- Orally and Nasal Inhaled Drug Products
- Total Organic Carbon (TOC)

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OINDP Services

- Pressurized Metered Dose Inhalers (pMDI)
- Nasal Sprays: aqueous, powder, and propellant driven
- Dry Powder Inhalers (DPI)
- Nebulizer: solutions and suspensions

Orally Inhaled and Nasal Drug Products

Critical Quality Attributes

- Delivered Dose (Emitted Dose) by means of Dosage Unit Sampling Apparatus (DUSA) to determine the total amount of drug emitted from the drug device and available to the user.

- Aerodynamic Particle Size Distribution (APSD) by means of Andersen Cascade Impactor and New Generation Cascade Impactor to determine the fine particle characteristics of the aerosol clouds generated by preparations for inhalation.

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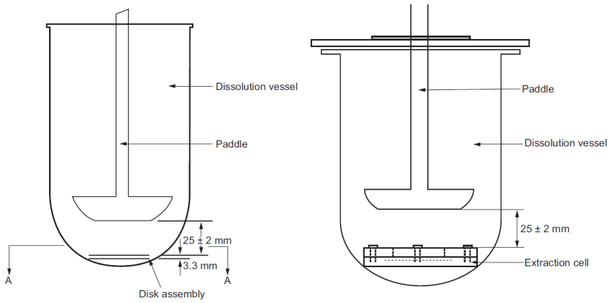
Transdermal Testing

Testing of TDDS from formulation development stage to routine analysis

CMC and Quality Control assessments & bioanalysis for clinical studies



Services provided:

General Quality Control Testing

- Assay
- Appearance
- Related substances

Transdermal Patches Specific Testing

- Active substance crystallization (qualitative detection)
- Residual solvents
- Extractables and leachables (E&L)
- Adhesive properties, upon specific request (peel force, adhesive strength and tack tests)
- Microbiology
- In-vitro release testing (IVRT) / Dissolution test
- Stability studies (ongoing and in-use, real-time storage and stress testing)

Bioanalysis Testing

- In-vitro permeation testing (IVPT)
- Preclinical and clinical studies for transdermal patches
- Bioanalytical quantification and pharmacokinetics

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Elemental impurities

ICP-MS semiquantitative screening to support the risk analysis

AAS testing for compendial Pharmacopoeia

2 instruments Agilent 7700 & 7800 and 2 digestors Ultrawave Milestone

Elemental impurities services

- Elemental Impurities analysis by ICP-MS according to ICH Q3D, Eur. Ph. and USP General Chapters <232>, <233> and <2232>
- Component approach (API, excipients, materials, supplies) or drug product approach.
- The 24 elements related in the ICH Q3D guideline (class 1, 2A, 2B, 3) and/or others required case by case.
- Different possible strategies:
  - Semi-quantitative screening
  - Limit Test Validation
  - Quantitative Method Validation
  - Sample analysis for quality control or ICH Q3D control strategies
- Elemental Impurities in Purified Water.
- If required full package, including risk analysis and toxicological evaluation.

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Nitrosamines

Screening and quantification of nitrosamines in API or DPs

LC-MS/MS Agilent 6490 Triple Quad and HS-GC-MS Agilent

Nitrosamine impurities services

- Limit test validation: Screening of target nitrosamines by LC-MS/MS or HS-GC-MS according to EMA and FDA recommendations.
- If required full package, including toxicological evaluation.
- Initial 30ppb default limits lowered to a current sensitivity of 1ppb.
- Development and validation of a quantitative method when any nitrosamine exceeds established limits.
- Up to 21 most common nitrosamines in a single run.
- Specific API-related nitrosamines.

1. N-Nitrosodimethylamine (NDMA)
2. N-Nitrosodiethylamine (NDEA)
3. N-Nitrosodisopropylamine (NDIPA)
4. N-Nitroso ethylisopropylamine (NEIPA)
5. N-Nitroso-n-methyl-4-aminobutyric acid (NMBA)
6. N-Nitrosopyrrolidine (NPYR)
7. N-Nitrosodi-n-butylamine (NDBA)
8. N-Nitroso Morpholine (NMOR)
9. N-Nitrosodiethanolamine (NDELA)
10. N-nitrosopiperazine (NPIP)
11. N-nitroso-N-methylaniline (NMA)
12. N-nitrosoethylmethylamine (NMEA)
13. N-Nitrosodiphenylamine (NDPhA)
14. N-nitrosodi-n-propylamine (NDPA)
15. N-nitroso-N-methylaniline (NMPA)
16. 1-Methyl-4-nitrosopiperazine (MeNP)
17. di-n-nitrosopiperazine (DNPZ)
18. 2-Nitroso-octahydrocyclopentapyrrole
19. N-nitroso-piperazine (MNPZ)
20. N-nitroso-varenicline (NNV)
21. 7-Nitroso-3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo-[4,3- a]pyrazine

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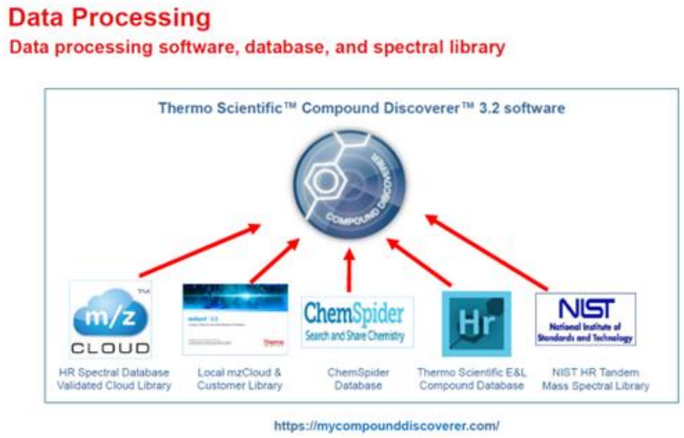
Extractables & Leachables

Orbitrap Exploris 120 Mass Spectrometer



Extractables & leachables testing services

- Full package, including risk analysis and toxicological assessment.
- Step by step approach from scratch or based on existing documentation from the packaging material supplier:

    1. Analytical Evaluation Threshold (AET) determination
    2. Extractables study (potential leachables)
    3. Simulation / migration studies (probable leachables)
    4. Risk Assessment (leachables selection)
    5. Toxicological assessment and QSAR studies (specs)
    6. Leachables study (confirmed leachables)

- Availability of a comprehensive pool of instruments: GC-MS with HS, GC-MS with ALS, HPLC-MS/MS, Orbitrap HRMS, ICP-MS, IEX-HPLC

08
CMC gen. services

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CMC general services

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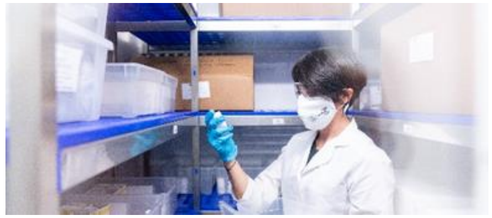
Stability Services

Over 100m3 in storage capacity, backup chambers and 2 EU sites



Climatic chamber storage at ICH zones II, IVb & more

- Standard conditions: 25ºC/60%RH; 30ºC/65%RH; 40ºC/75%RH
- Tropical conditions (zone IVb): 30ºC / 75%RH
- Other conditions: 25ºC/40%RH; 30ºC/35%RH; 40ºC/NMT 25%RH
- Refrigerated conditions: 5ºC
- Freezing conditions: - 20ºC; - 80ºC
- Semipermeable and personalized conditions on demand

Stability testing

- ICH stability testing (long-term, intermediate, accelerated)
- Ongoing stability programs
- Preliminary stability and compatibility studies
- Development & Validation of stability-indicating methods
- Stress testing (light, pH, humidity, temperature, oxidation)
- Photostability of drug substances and drug products
- Determination of leachables migrated from packaging
- In-use stability : multidose containers, parenteral solutions
- Holding time studies for bulk products
- Temperature cycle test, freeze-thaw, transportation
- Full study management

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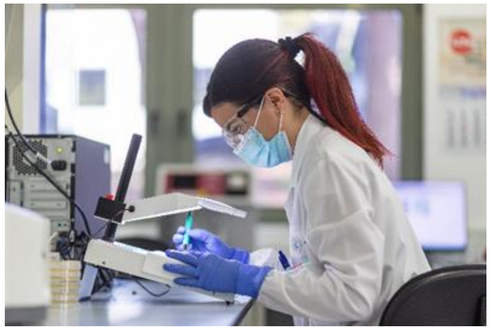
Microbiology Testing

active ingredients
human and veterinary DPs
excipients
intermediates
IMP



Non-sterile testing

- Microbial limit test (TAMC, TYMC, and pathogens)
- Total viable spore count

Sterile testing

- Sterility Testing (isolator Getinge + Steritest pump)

Endotoxins

- Chromogenic LAL and recombinant (Trillium®)
- Gel Clot
- Turbidimetric

Other services

- Particulate matter (visible and subvisible particles)
- Water and environmental microbiological monitoring
- Growth promotion testing of culture media
- Antibiotic microbiological assays, method dev & validation
- Suitability and validation of microbial and sterility tests
- Challenge tests (LAL and gel clot)
- Run Media Fill (small batches)
- Antimicrobial effectiveness testing
- Biocides effectiveness
- Other tests for injectables (pH, osmolarity…)

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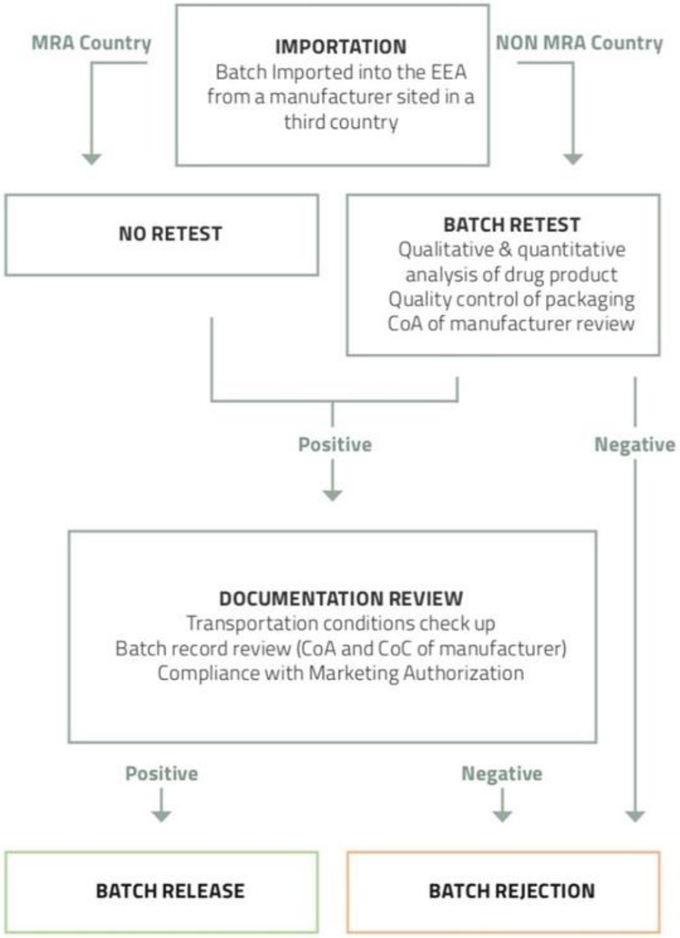
Batch Testing & Batch Release



Batch Testing

- Analytical method transfer (AMT)
- Batch testing of clinical and marketing batches according to CoA
  Individual or full parameter analysis for batch CoA according to relevant pharmacopoeia

Importation and Support activities

- Request of importation license to AEMPS
- Importation into the EU of DPs (human, veterinary or IMPs)
- Warehousing, EU depot and shipment (logistic partner)
- Qualified Person Declaration for IMPs and DPs (3 QPs)
- Manufacturing chain audit (EU-GMP compliant partner)
- Product Quality Review (PQR) yearly review

Batch Release

- Certificate of Analysis for Release
- OOS, deviations, CAPAs and change control management
- Batch manufacturing record review
- Batch release in accordance with Marketing Authorization

09
CMC biologics

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CMC of biologics

peptides
hormones
interferons
insulins
coagulation factors
mAbs
biosimilars
toxins
ADCs
heparins
vaccines

Quality Control of Biologics

- Routine batch testing and release of biological DPs.
- Compendial pharmacopoeia methods, pre-qualified methods, client's method transfer or ex-novo development.

Characterization of new Biologics

- Innovative biologics.
- Comprehensive analytical fingerprinting.
- Integrated analytical model using multiple techniques.

Comparability studies (aka biosimilarity assessment)

- Biosimilars.
- According to the ICH Q6B guideline on global comparability.
- Step-by-step approach oriented to critical quality attributes (CQA)

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CMC of Heparins and other Glycosaminoglycans

Unfractioned heparins
Low molecular weigh heparins (LMWH)
Heparan sulphate
Chondroitin sulphate
Dermatan sulphate
Other heparinoid related substances

Structural characterization

- Disaccharides building blocks (fully hydrolyzed samples)
  - Capillary electrophoresis with laser-induced fluorescence
  - Ion Exchange Chromatography
- Higher order saccharides building blocks (partially hydrolyzed samples)
  - Reverse phase liquid chromatography coupled to mass spectrometry

Interaction characterization

- Antithrombin affinity chromatography
- Binding to Antithrombin by Surface Plasmon Resonance
- Binding to PF4 protein by Surface Plasmon Resonance

Potency assays - Chromogenic methods

- Anti-factor IIa
- Anti-factor Xa

Quality Control of batches and comparability studies

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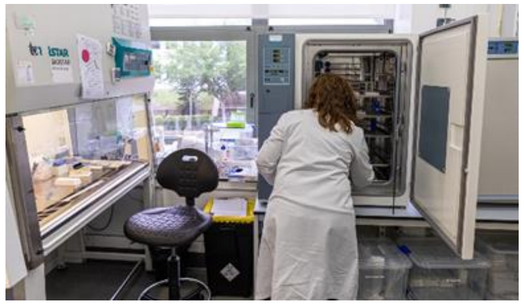
CMC of vaccines

human & veterinary
infectious & allergy
BSL Level 1 and 2,
non-living, & recombinant



Characterization of vaccine ingredients

- Antigen characterization (FDA Guideline for Vaccines or related Products)
- Adjuvant characterization (EMA Guideline on Adjuvants in Vaccines for Human Use)
- Determination of preservatives and other excipients

Potency assay of vaccines

- Development from scratch and validation
- Method transfer to client or routine quality control
- In vivo immunization in different species
- Relevant antigen determination by immunoassay
- Activity determination by competitive immunoassay

Characterization of In-House Reference Preparations (IHRP)

Quality Control of batches

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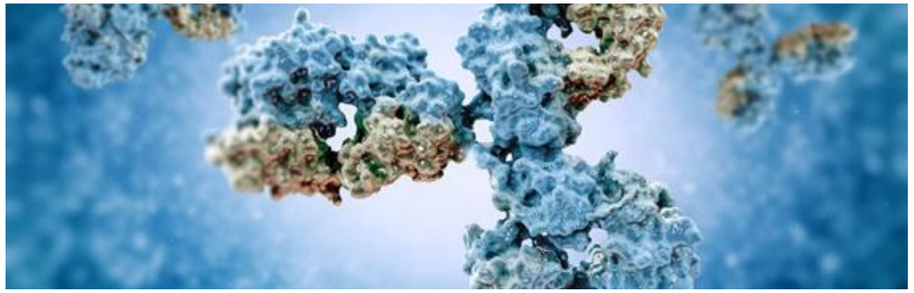
Quality Control of Biologics

Pre-qualified methods

- Insulin
- Interferons
- Coagulation factors
- Filgrastim and PEG-Filgrastim
- Hormones: GSF, FSH, LH, hCG, GCG, GLP1, GH, TSH
- Heparins: Unfractionated heparins and Low-molecular-weight heparin (LMWH)
- Monoclonal Antibodies: Adalimumab, Bevacizumab, Infliximab, Omalizumab, Ranibizumab, Rituximab, Trastuzumab, Regdanvimab, Denosumab, Oregovomab, Aflibercept



Analytical Method Transfer (ICH/USP compliant)

- Key for a successful batch testing project.
- Comparative testing, Co-validation, Revalidation or Transfer Waiver.
- Document exchange, writing (SOPs, protocols)
- Compendial methods: Verification (transfer waiver)
- Non-compendial methods: Training & shakedown run, revalidation, batch analysis comparison.

Batch Testing

- Physical-chemical: Identity, purity, quantification, impurities
- Formulation: Appearance, pH, osmolality, particulate matter.
- Immunology and cell-based assays: Biological potency assays.
- Microbiology: Endotoxins and sterility.
- Specific Tests (case by case).

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Quality Control of Biologics

- Identifications (IEF, IEX-HPLC, ELISA, peptide mapping, glycosylation profile ciIEF)
- Appearance (color, clarity)
- Assay (ELISA, SEC-HPLC, RP-HPLC) and dosage uniformity
- Purity (CE-SDS -reduced and non-reduced, SEC-HPLC, RP-HPLC)
- Protein Content (UV, 280nm, Bradford, BCA, Lowry)
- Dosage of excipients (HPLC)
- Physical determinations: pH, osmolality, moisture (Karl Fisher)
- Residual solvents (volatile organic compounds & impurities)
- Impurities identification (HPLC, LC-MS)
- Process-related impurities determination (ELISA, RT-qPCR)
- Elemental impurities (AAS, ICP/MS)
- Nitrosamine impurities (LC-MS-MS, HS-GC-MS)
- Particulate matter (visible and subvisible particles)
- Extractables & Leachables
- Enzymatic and chromogenic tests (heparins and others)
- Biological potency assays (CBA, ELISA, flow cytometry)
- Extractable volume
- Physical properties of injection devices (glide & brake force)

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Characterization & Comparability

General Analytical Techniques (preliminary overview)

- Electrophoresis: PAGE, SDS-PAGE, Bioanalyzer, IEF
- Western Blot
- Extinction Coefficient, Bradford, Lowry, BCA (total protein quantitation)
- HPLC AccQ-Tag® (Waters) and OPA® (Agilent) for amino-acid analysis
- Sulfide quantitation by Ellman method
- Antibody isotyping

Structural Analysis (complete identification)

- Intact protein mass determination (Electrospray MS and MALDI-TOF)
- Peptide mapping: amino acid sequencing, disulfide bonds and post-translational modifications (LC-UV-MS/MS) (QTof and QTRAP)
- N and C terminal sequencing of intact protein (MALDI-TOF and Edman degradation)
- Glycosylation and phosphorylation sites (LC-UV-MS)
- Glycosylation Profiles: sialic acid, charge and glycan profiles (LC with fluorescence detection and MS/MS, capillary electrophoresis with LIF detection)
- Monosaccharide profile (LC and GC)

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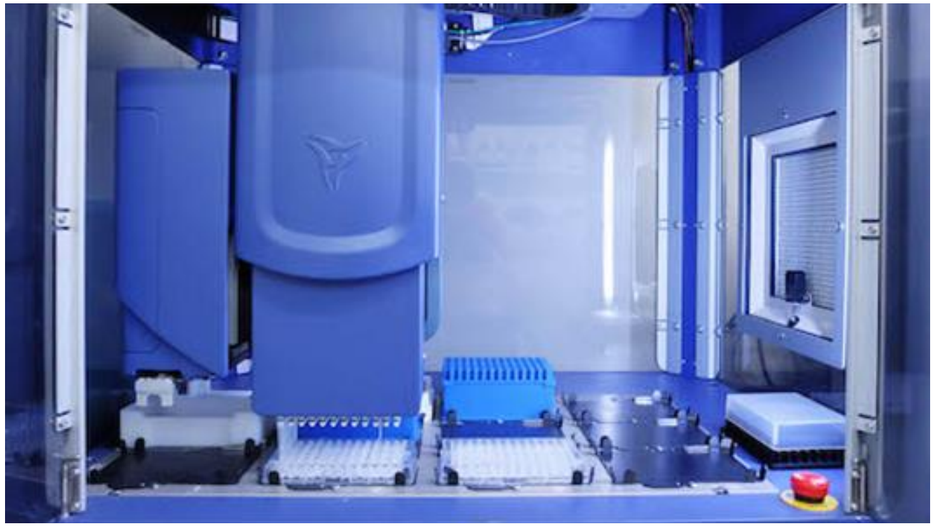
Characterization & Comparability

Conformational Analysis

- Circular Dichroism (CD)
- Ultraviolet spectroscopy (UV)
- Fluorescence spectroscopy (FL)
- Infrared spectroscopy (FTIR)



Biological Activity

- Binding studies by ELISA, ECLA (MDS) and SPR (Biacore)
- Potency assays using cell –based assays: From primary cell lines, immortalized cell lines or commercial arrested cell lines.
- Competitive inhibition ELISA assays for vaccines.

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CMC biologics

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Characterization & Comparability

Identity, Content and Protein-Related Impurities

- Liquid chromatographic patterns:
  - RP-HPLC/UPLC
  - SEC-HPLC/UPLC
  - Ion Exchange-HPLC/UPLC
  - Affinity-HPLC/UPLC
  - LC coupled to UV (VWD, DAD), fluorescence, refractive index, evaporative light scattering, electrochemical, charged aerosol and MS detectors.
- Capillary electrophoresis
- Imaged capillary isoelectric focusing (icIEF)
- ELISA and ECLA immunoassays

Process-Related Impurities

- Host Cell Proteins: specific ELISA development
- Chemical contaminants by HPLC and GC
- Elemental impurities by AAS and ICP-MS
- Nitrosamine impurities by LC-MS/MS and HS-GC-MS
- DNA by colorimetric and qPCR commercial kits
- Mycoplasma by PCR commercial kits
- Endotoxins by Colorimetric test
- Bioburden

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