Eurofins ADME Bioanalyses

2021 services

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End-To-End Integrated Lab Performance

Eurofins Group

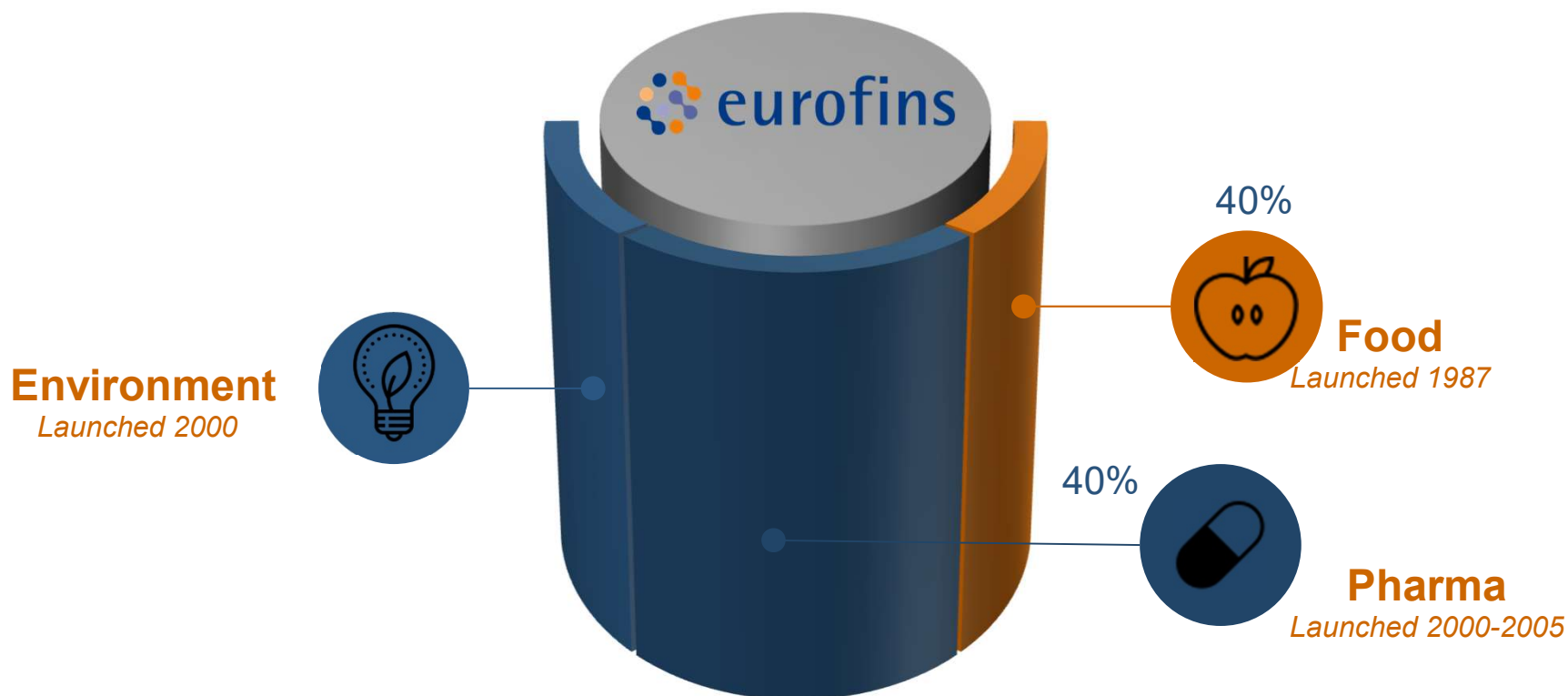**Supporting DMPK from screening to registration**

Eurofins' Mission

To contribute to global Health, Safety & Environment with the best in bioanalysis

Environment
Launched 2000

40%
Food
Launched 1987

40%
Pharma
Launched 2000-2005

Eurofins main figures

Over 400 million tests performed each year

Over 45,000 employees

Network of more than 800 laboratories in 47 countries

Founded in 1987 Became the world leader in Bioanalysis
IPO in 1997 in Paris
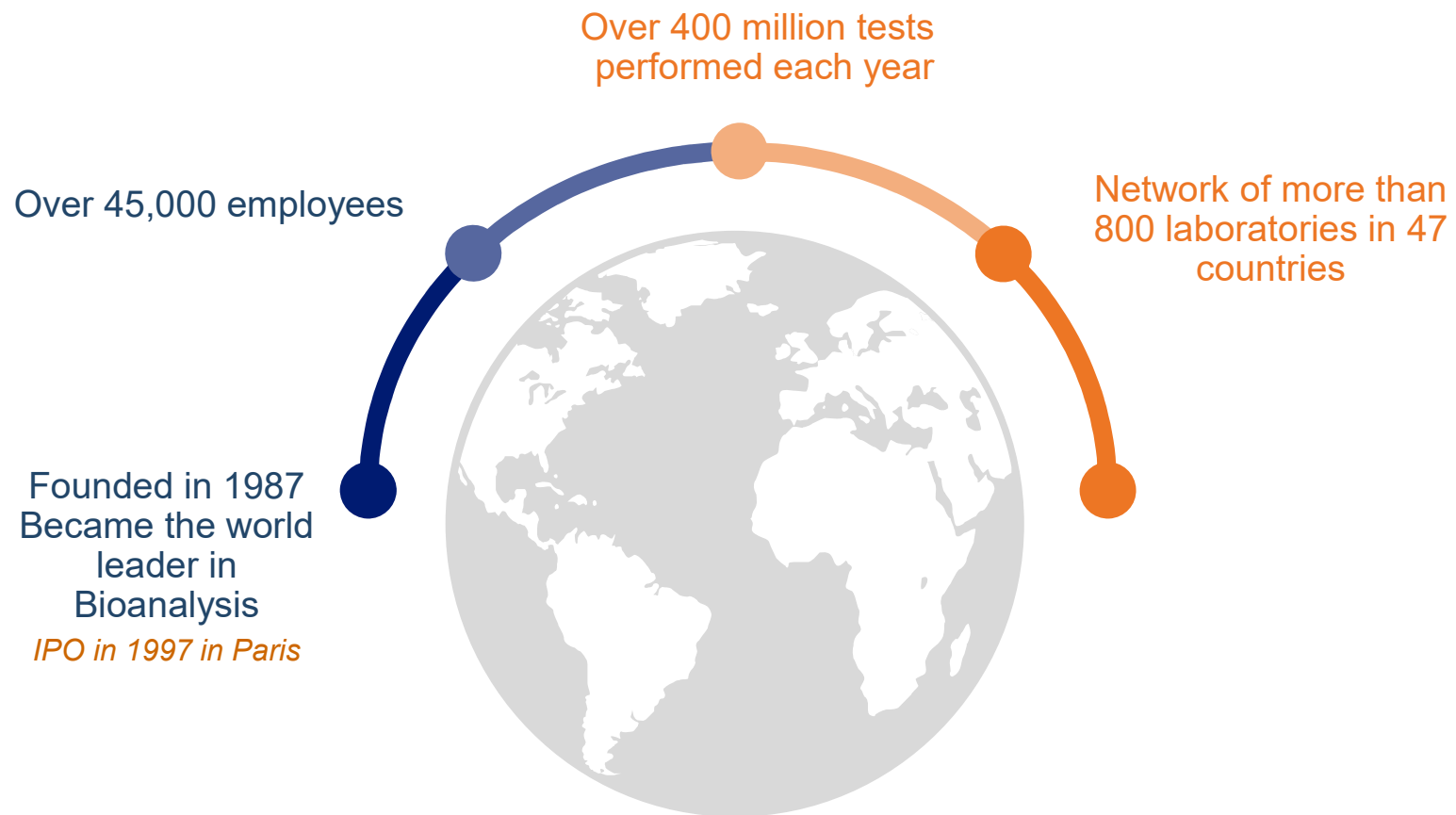
An international network of world class laboratories

eurofins | **ADME BIOANALYSES**

Supporting DMPK from screening to registration

Laboratories
- ■ Food & Feed Testing
- ■ BioPharma Services
- ■ Clinical Diagnostics
- ■ Agroscience Services
- ■ Genomic & Forensic Services
- ● Consumer Product Testing
- ■ Environment Testing
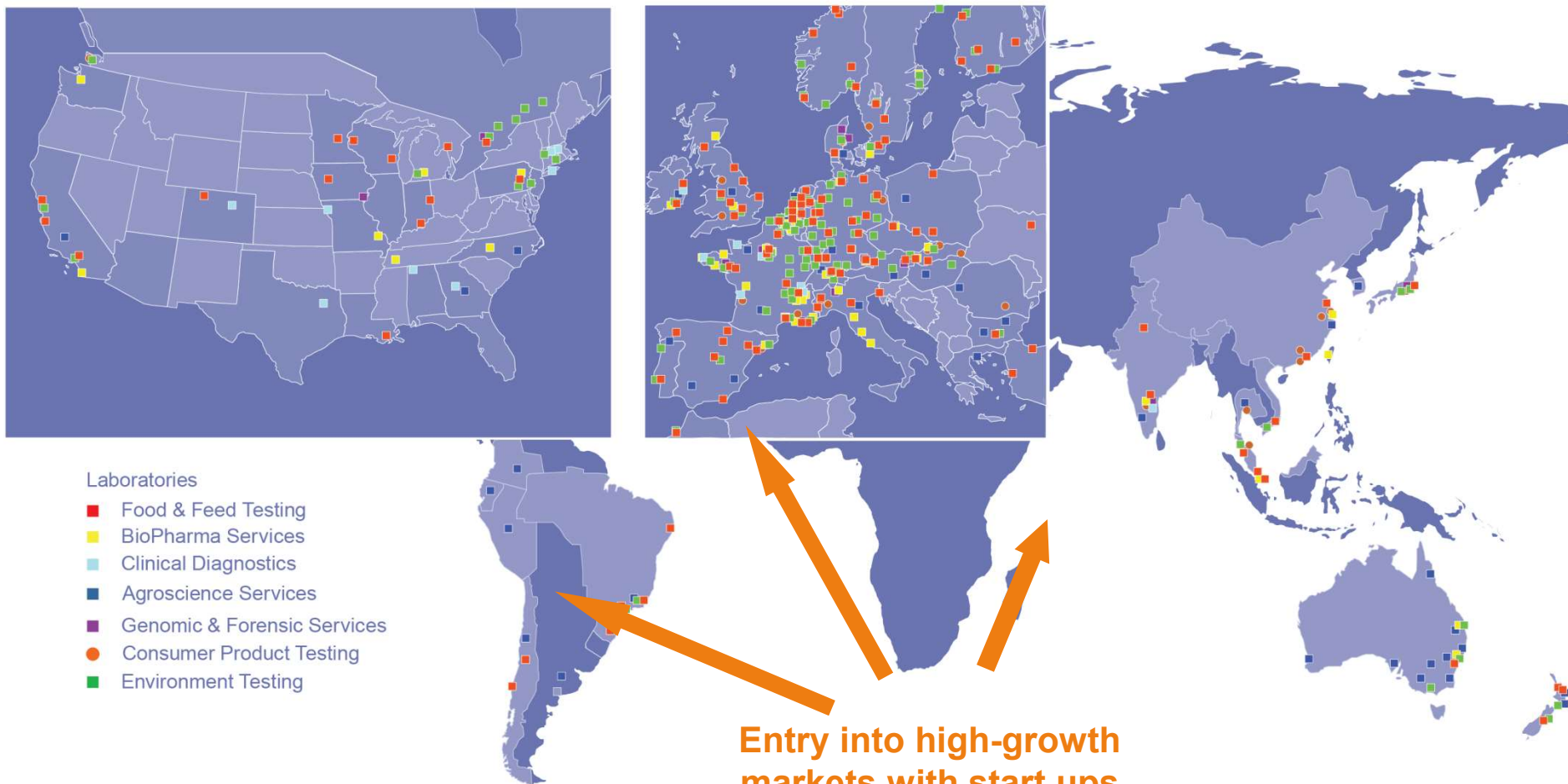
Entry into high-growth markets with start ups & acquisitions

5

Pharmaceutical services

EUROFINS BIOPHARMA SERVICES

- **Discovery**
- **Early development**
- **Bioanalytical services**
- **Central lab**
- **Product testing**
- **Genomics**
- **Human safety testing**
- **Clinical diagnostics**
- **Medical device testing**
- **Cosmetic testing**
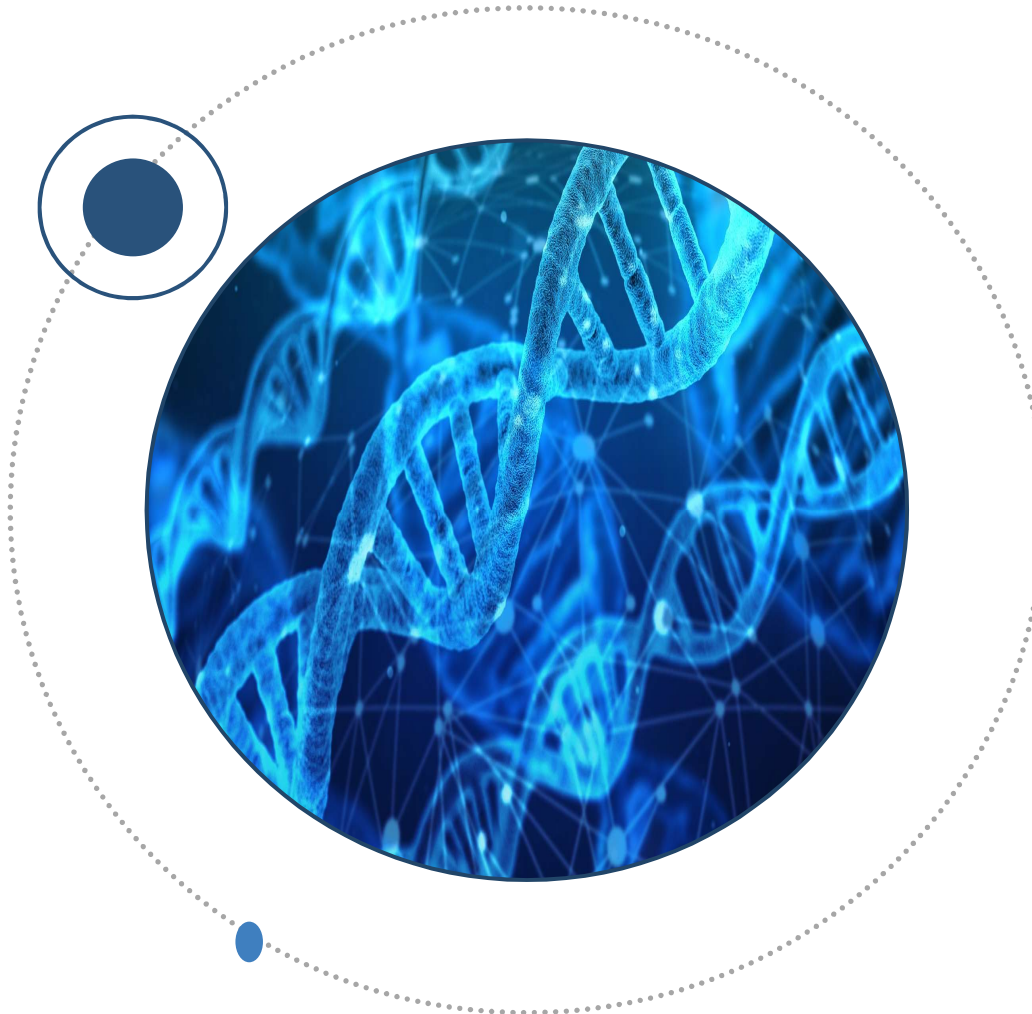
Eurofins ADME Bioanalyses Vergèze, France

Supporting DMPK from screening to registration

Strengths | Project management

- **Dedicated project manager, single point of contact**

- **Agile management to commit to defined timelines**

- **Resources allocated to match the study timelines**

- **In-built quality control on all assays and analyses**

- **KPIs**

★ **Quotation within 48h of receipt of comprehensive RFP, (>95% in last 3 years)**

★ **Results despatch 2 weeks from end of analysis**

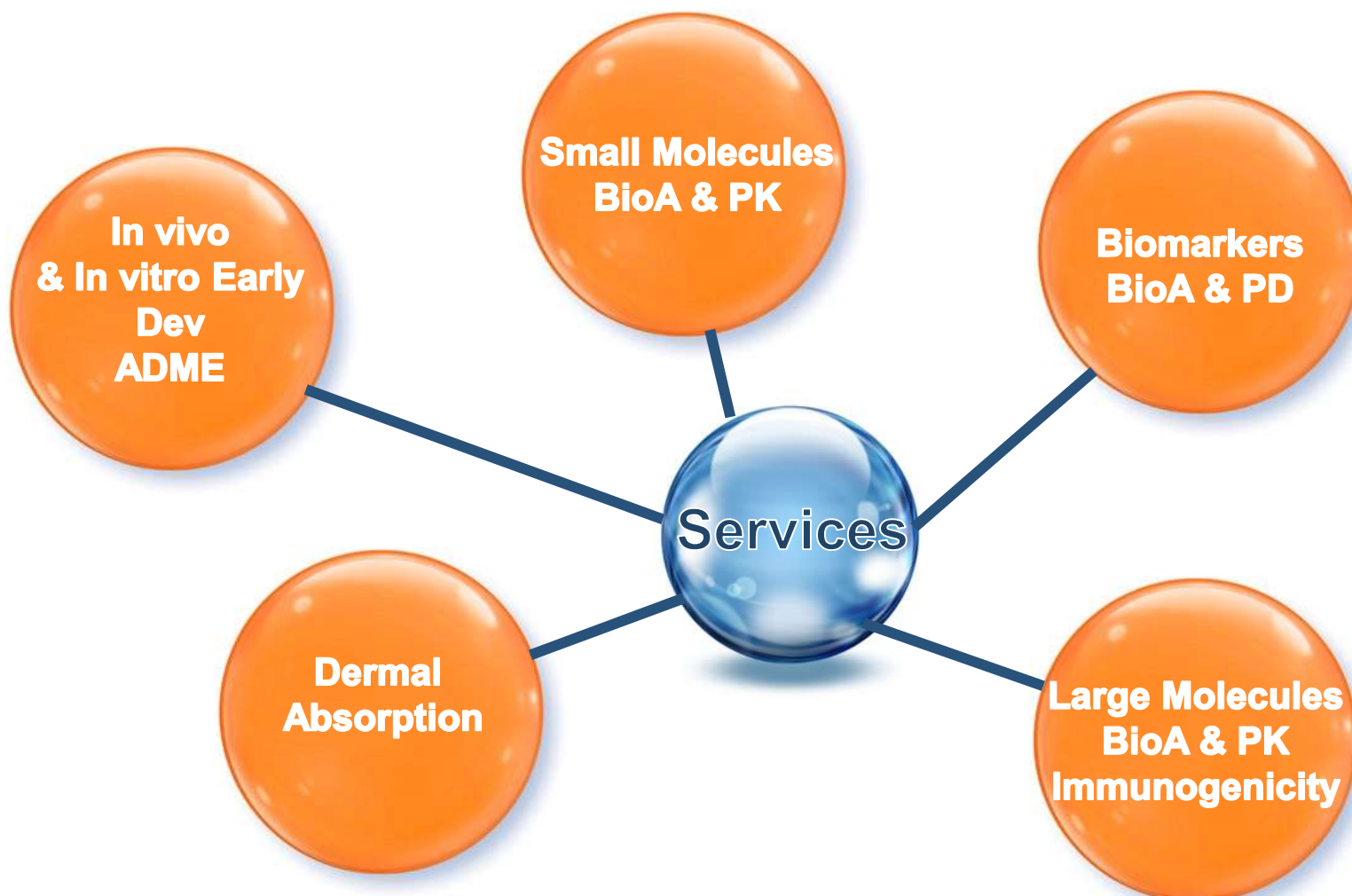★ **Report despatch 2 weeks from results despatch**

Overview | Company

eurofins | **ADME BIOANALYSES**
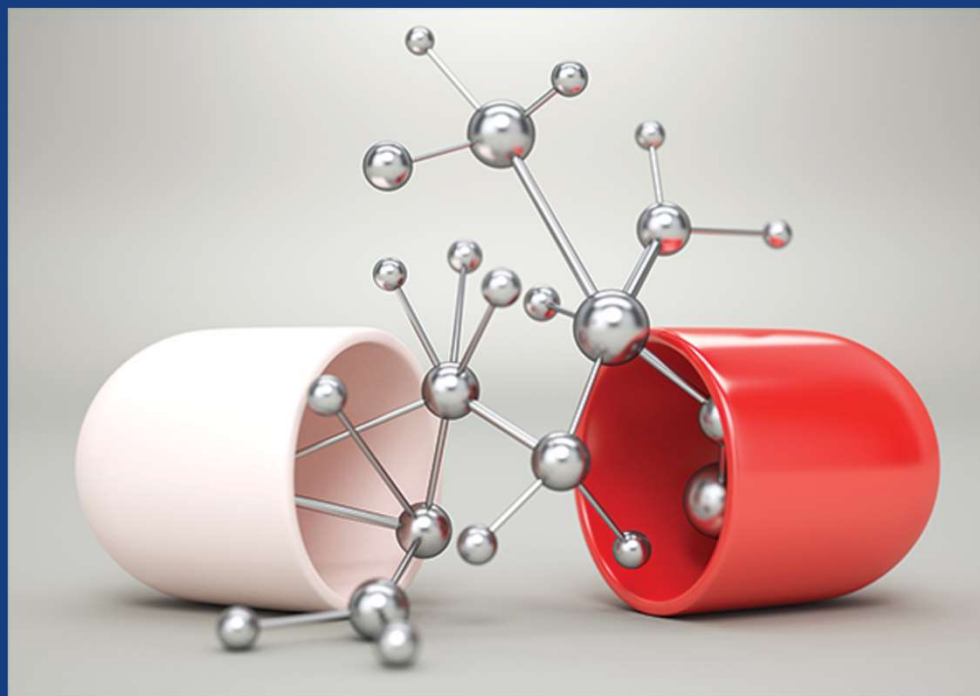
Supporting DMPK from screening to registration

→ Early Stage → Pre-clinical → Phase I & II → Phase III → Post-marketing

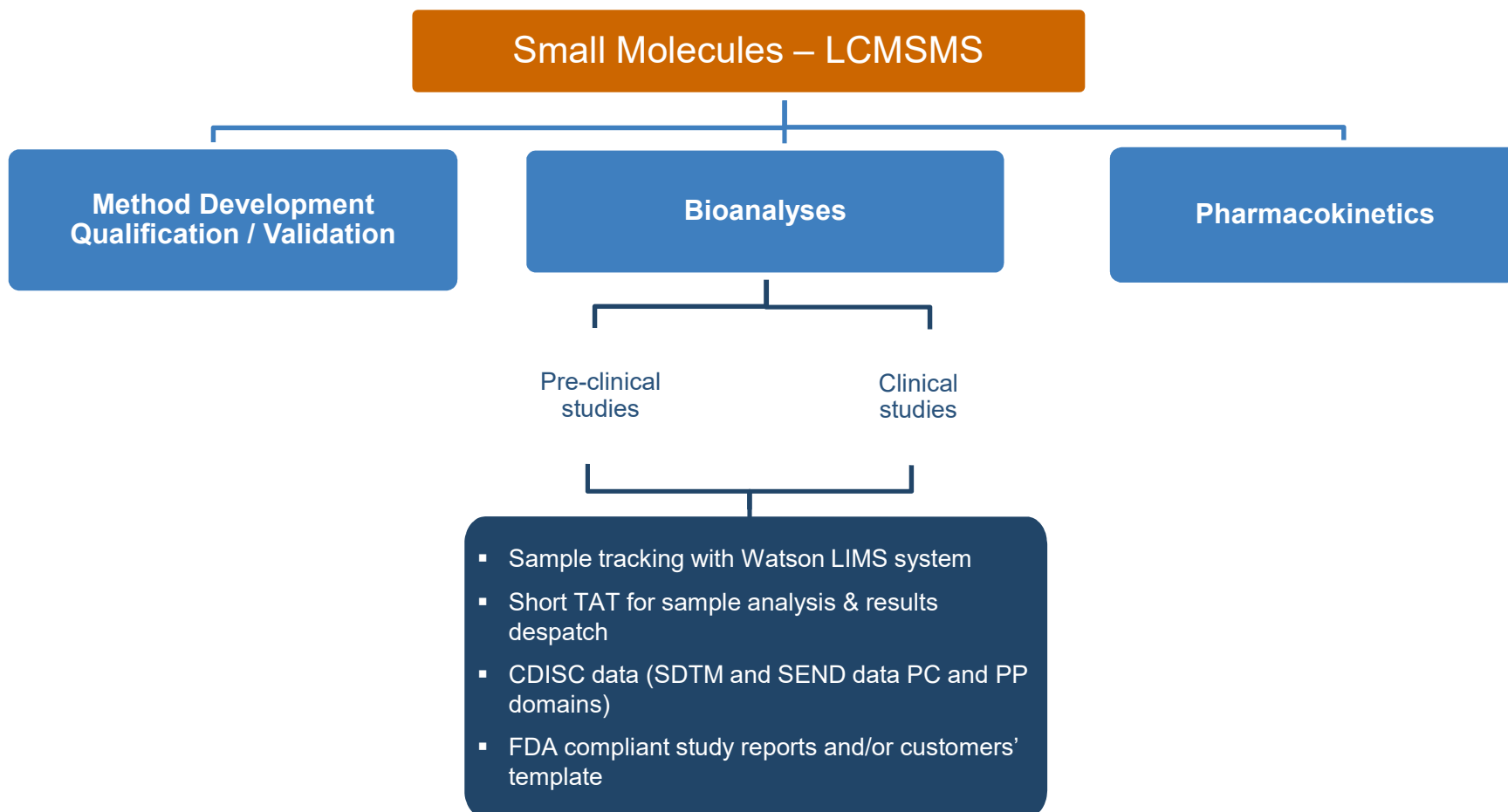**In vivo & In vitro Early Dev ADME**

Small Molecules BioA & PK

Biomarkers BioA & PD

Services

Dermal Absorption

Large Molecules BioA & PK Immunogenicity

9

Small Molecules

Supporting DMPK from screening to registration

Small Molecules | Overview

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Supporting DMPK from screening to registration

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                    ┌─────────────────────────────┐
                    │   Small Molecules – LCMSMS   │
                    └─────────────────────────────┘
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Method Development Qualification / Validation	Bioanalyses	Pharmacokinetics

Pre-clinical studies   Clinical studies

- Sample tracking with Watson LIMS system
- Short TAT for sample analysis & results despatch
- CDISC data (SDTM and SEND data PC and PP domains)
- FDA compliant study reports and/or customers' template

In vitro & In vivo Early Development ADME studies

Supporting DMPK from screening to registration

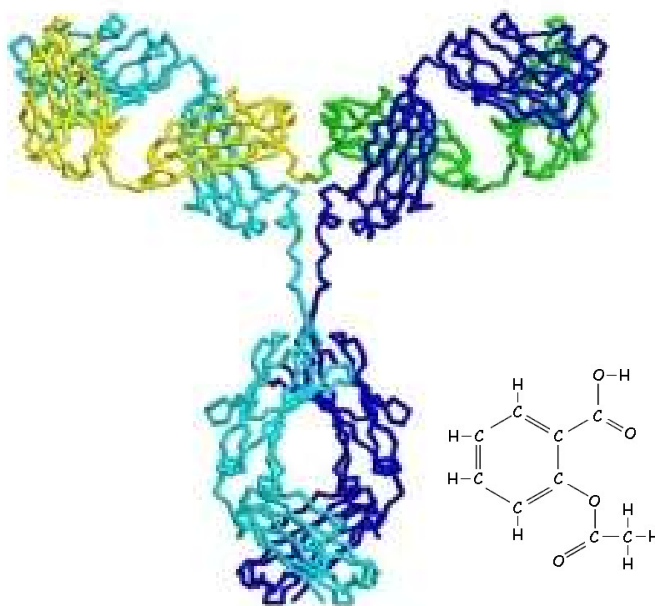# Early development - *In vitro / In vivo*

- ## *In vitro* studies:

  - *In-vitro* metabolism and distribution

  - Sample analysis cold/radioactive

- ## *In vivo* studies:

  - Animal facilities for rodents, other species in partnership

  - Early screening tests and exploratory PK

  - Radiolabelled/cold compound
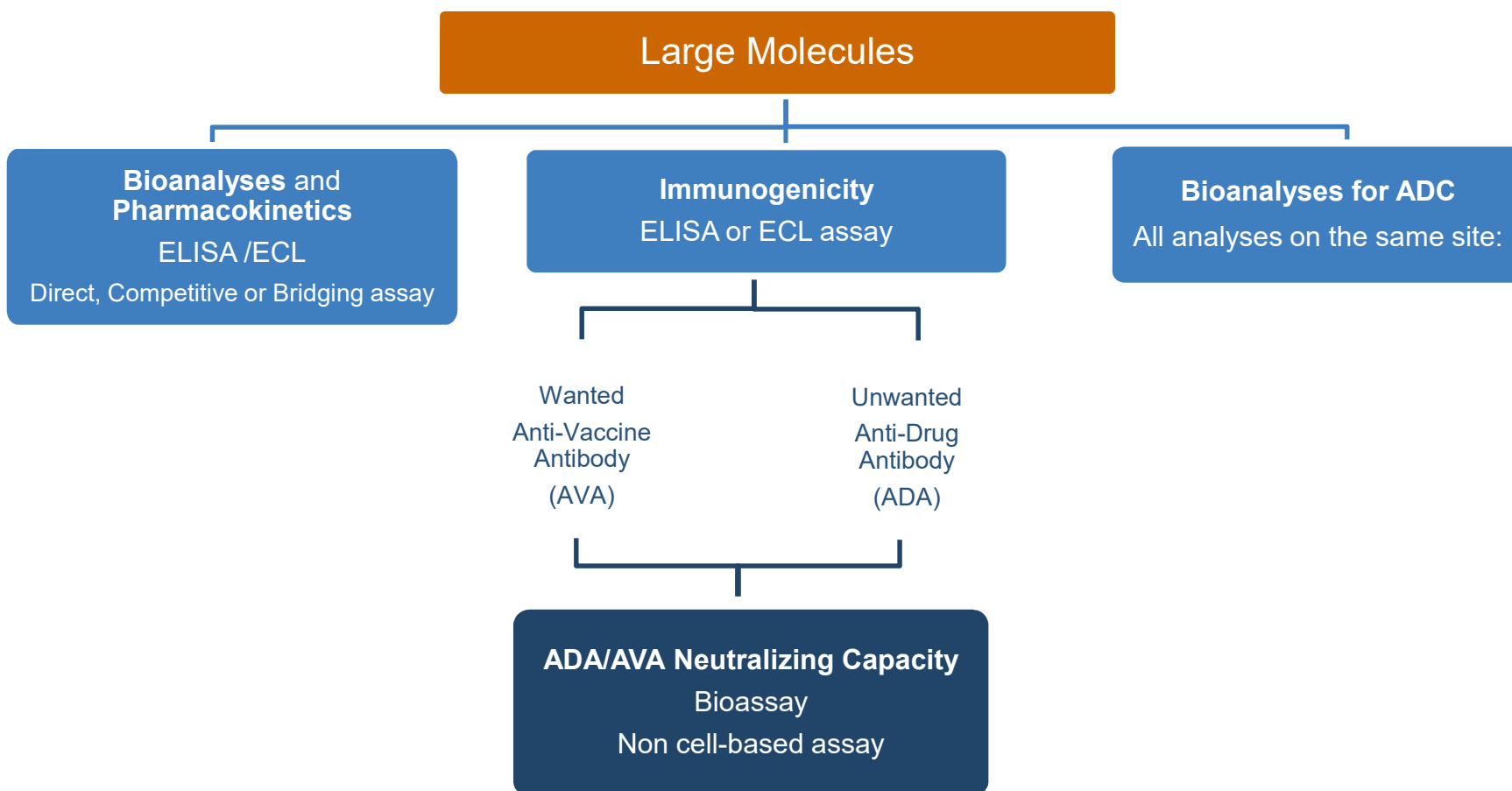
  - ADME

Large Molecules

Supporting DMPK from screening to registration

Large molecules | Overview

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Supporting DMPK from screening to registration

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                        ┌─────────────────────────┐
                        │     Large Molecules     │
                        └─────────────────────────┘
```

Bioanalyses and **Pharmacokinetics**	**Immunogenicity**	**Bioanalyses for ADC**
ELISA /ECL	ELISA or ECL assay	All analyses on the same site:
Direct, Competitive or Bridging assay		

Wanted
Anti-Vaccine
Antibody
(AVA)

Unwanted
Anti-Drug
Antibody
(ADA)

ADA/AVA Neutralizing Capacity
Bioassay
Non cell-based assay

Dermal absorption / Drug release testing

Supporting DMPK from screening to registration
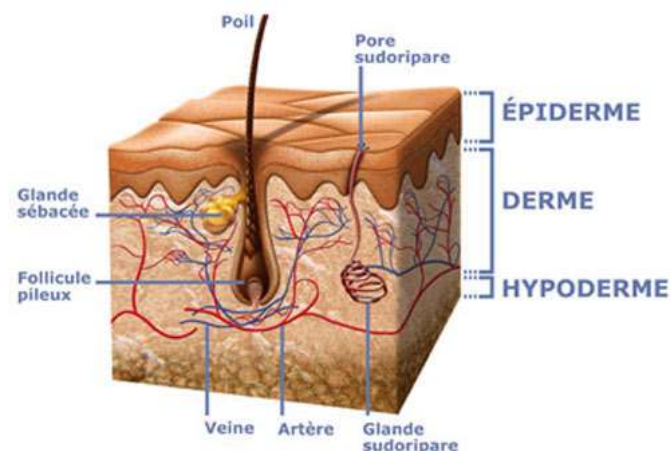
Dermal absorption / Drug release testing

- **_In vitro_ evaluation of topical formulations**

  - Human skin from aesthetic surgery/synthetic membrane

  - Drug release/dermal absorption

  - Early Research
    - compound selection
    - formulation comparisons

  - Regulatory studies
    - risk assessment
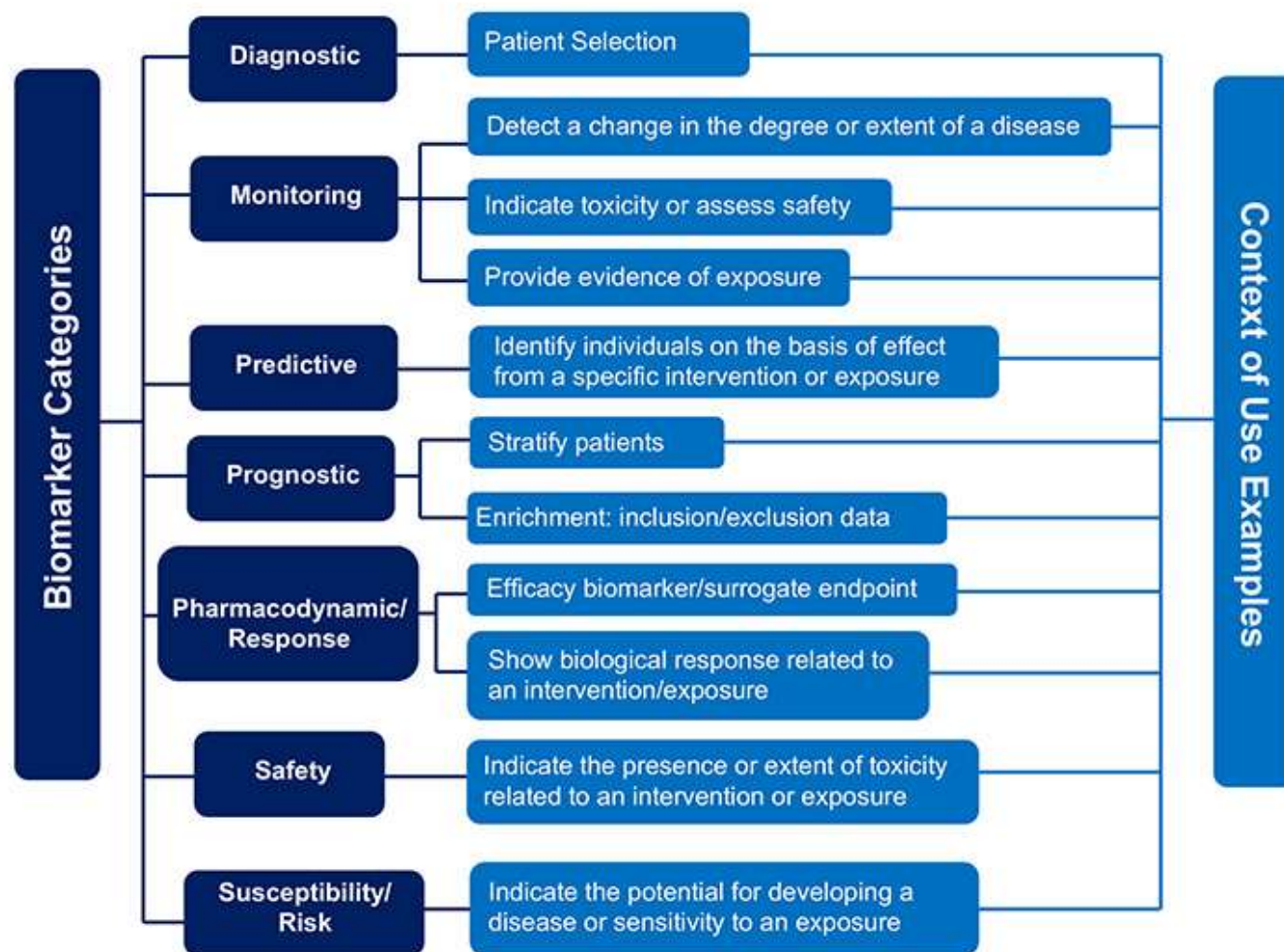   - drug release
    - equivalence

17

Biomarkers

Supporting DMPK from screening to registration

Biomarkers

Context Of Use

Supporting DMPK from screening to registration

Biomarker Categories

- **Diagnostic** → Patient Selection
- **Monitoring** → Detect a change in the degree or extent of a disease
  → Indicate toxicity or assess safety
  → Provide evidence of exposure
- **Predictive** → Identify individuals on the basis of effect from a specific intervention or exposure
- **Prognostic** → Stratify patients
  → Enrichment: inclusion/exclusion data
- **Pharmacodynamic/ Response** → Efficacy biomarker/surrogate endpoint
  → Show biological response related to an intervention/exposure
- **Safety** → Indicate the presence or extent of toxicity related to an intervention or exposure
- **Susceptibility/ Risk** → Indicate the potential for developing a disease or sensitivity to an exposure

Context of Use Examples

19

https://www.fda.gov/drugs/biomarker-qualification-program/context-use

Biomarkers

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Panels & Services

Supporting DMPK from screening to registration

Biomarkers measurement in biofluids

- Scientific expertise for BMK selection, BMK network; gold standard BMKs

- Robust method development (qualification, validation); immunoassays, LC-MSMS

- Expertise in multi-analytes analytical method (multiplex, screening of cytokines)

- Serum, plasma, urine, CSF, bronchoalveolar, synovial fluids but also tissues with soluble analytes extraction)

- Small and large BMKs: proteins, peptides, metabolites, hormones, etc…

- High quality reports FDA / EMA guidelines compliant; BMKs database

Main clinical areas/ biological processes spanned by our assays

Neurology
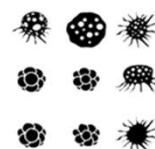
Oncology

Metabolic disorders & liver diseases

Inflammation

Tissue modeling/scarring

Oxydative stress

Microbiota

Eurofins ADME Bioanalyses is constantly expanding its menu with new biomarker panels according to customer needs.

Biomarkers

Neuro ATN panel – short list BMKs

Amyloidopathy: **Aß42, Aß40, ratio Aß42/Aß40**

Tau pathophysiology: **P-tau181**

Neurodegeneration: **Total-tau**
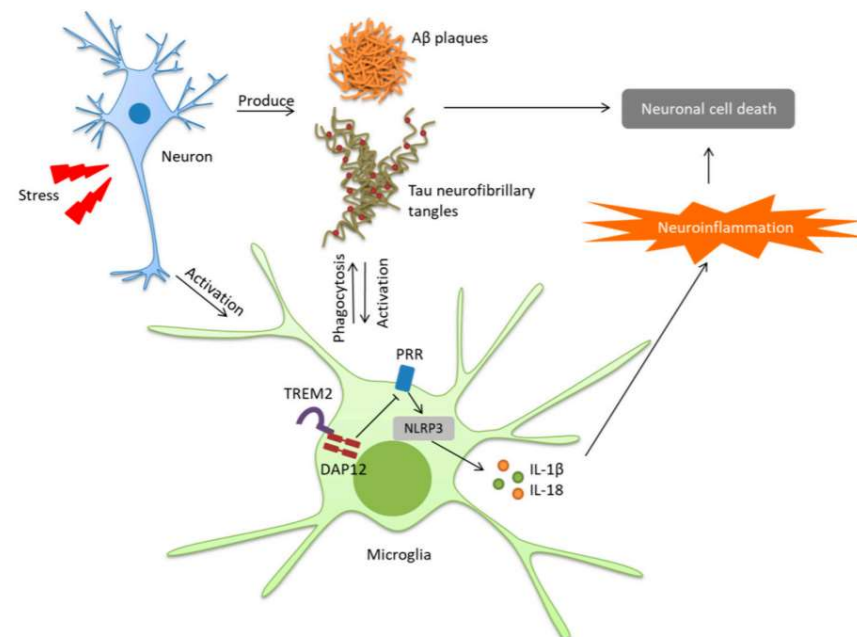
Axonal damage: Neurofilament –Light NfL

Synucleopathy: alpha-Synuclein

Synaptic dysfunction: Neurogranin

Microglial responses: sTREM2

Astrogial-related responses: GFAP, YKL40, S100

Neuroinflammation: Interleukins, Chemokines

Dong et al., imjs, 2019

Large panel of BMKs available / CNS diseases specific panels
Possibility of multiplex development

Biomarkers

Liver & inflammation panel

Fibrotest: Haptoglobine, Apolipoprotéin A1, Alpha 2 macroglobuline, Bilirubin total & GGT

ELF test: HA, TIMP1, P3NP

Other: CK18 M30, CK18 M65, CXCL10, IL8, YKL40

Inflammation panels: Interleukins, Chemokines (multiplex analyses)

Metabolic panel: adipokines (leptin, adiponectin, GLP1 etc…)

HALLMARKS OF NASH

Steatosis   Inflammation   Ballooning   Fibrosis
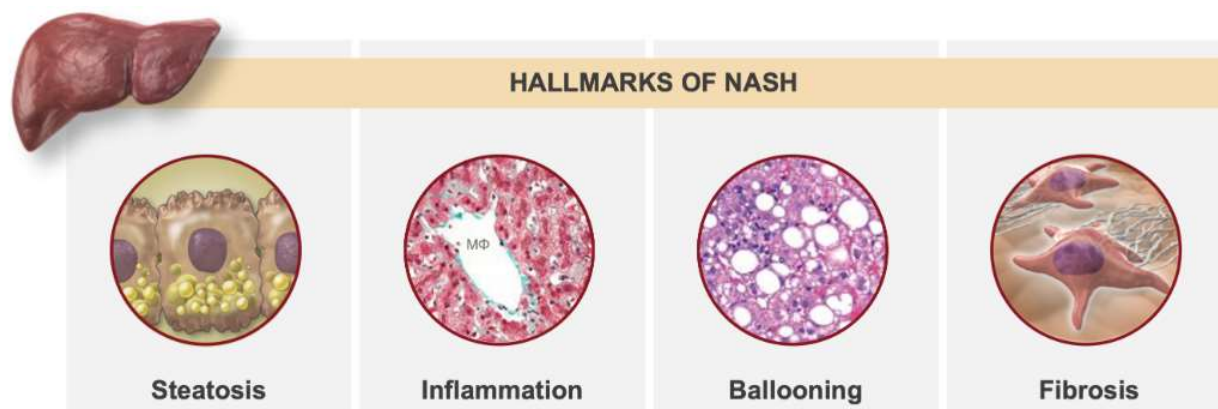
Biomarkers

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Immuno-Oncology – BMKs panels

111-Plex

BAFF, BAFF-R/TNFRSF13C, BCMA/TNFRSF17, BDNF, CD20, CD27, CD28, CD40L (soluble), CD276/B7-H3, C-Peptide, CTACK, CTLA-4, ENA-78, Eotaxin, Eotaxin-2, Eotaxin-3, EPO, FGF (basic), FGF-23, FLT3L, Fractalkine, FSH, G-CSF, Ghrelin (active), Ghrelin (total), GIP (active), GIP (inactive), GIP (total), GITR, GITRL, GLP-1 (active), GLP-1 (inactive), GM-CSF, gp130 (soluble), Granzyme A, Granzyme B, GRO-α, HAVCR2/TIM-3, I-309, IFN-α2a, IFN-β, IFN-γ, IL-1α, IL-1β, IL-1RA, IL-2, IL-2Rα, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12/IL-23p40, IL-12p70, IL-13, IL-15, IL-16, IL-17A, IL-17A/F, IL-17C, IL-17D, IL-17E/IL-25, IL-17F, IL-18, IL-21, IL-22, IL-23, IL-27, IL-29/IFN-λ1, IL-31, IL-33, Insulin, IP-10, I-TAC, LAG3, Leptin, Luteinizing Hormone (LH), MCP-1, MCP-2, MCP-4, M-CSF, MDC, MIF, MIP-1α, MIP-1β, MIP-5, OX40, PD1 (epitope 1), PD1 (epitope 2), PD-L1 (epitope 1), PD-L2, PlGF, PP, Proinsulin, PYY (total), RANKL/TNFSF11, SDF-1α, Tie-2, TIGIT, TLR1, TNF-α, TNF-β, TPO, TRAIL, TSLP, VEGF-A, VEGF-D, YKL-40

54-Plex

CRP, Eotaxin, Eotaxin-3, FGF (basic), GM-CSF, ICAM-1, IFN-γ, IL-1α, IL-1β, IL-1RA, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-8 (HA), IL-9, IL-10, IL-12/IL-23p40, IL-12p70, IL-13, IL-15, IL-16, IL-17A, IL-17A/F, IL-17B, IL-17C, IL-17D, IL-21, IL-22, IL-23, IL-27, IL-31, IP-10, MCP-1, MCP-4, MDC, MIP-1α, MIP-1β, MIP-3α, PlGF, SAA, TARC, Tie-2, TNF-α, TNF-β, TSLP, VCAM-1, VEGF-A, VEGF-C, VEGF-D, VEGFR-1/Flt-1 | Human

Single plex or multiplex analysis / Screening and test development
Immune checkpoints / Apoptose inhibitors / Tissue modeling / Inflammation
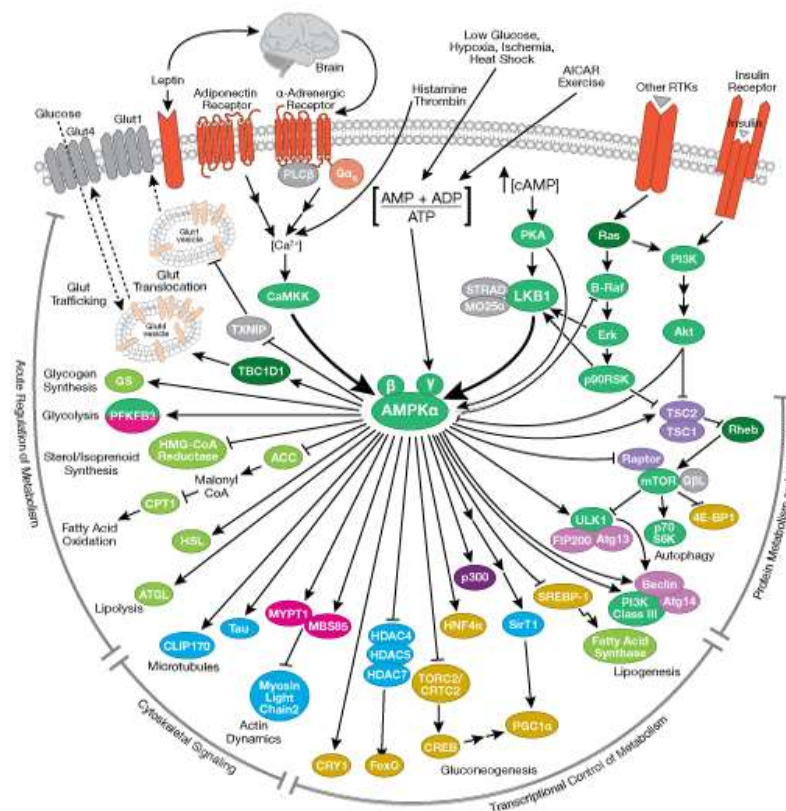
Biomarkers

Metabolic panel – short list BMKs

Supporting DMPK from screening to registration

C-peptide
Total GIP
Glicentin
GLP-1
Glucagon
Insulin
Iso-Insulin
MPO
Oxidized LDL
Proinsulin
Lispro
Lp(a)
FABPs
Leptin
Adiponectin
Apolipopoteins

Large panel of BMKs available / metabolic diseases specific panels
Possibility of multiplex development

Biomarkers

Microbiome

CE-marked microbiotatest onLuminex®200 IVDD 98/79/ EC

o Dysbiosis test

o A true numerical scoring system

o Monitoring the effects of antibiotics and ageing

o Guiding treatment in IBS disease

o Clinical significance of identifying and quantifying dysbiosis

o Forty eight preselected and documented bacterial targets of importance for gut health, covering >300 bacteria.

o Normal population established and incorporated into algorithms for

o Dysbiosis Index and bacteria abundance.

Biomarkers

Immunoassays

ELISA

chemiluminescence
colorimetry
fluorescence

plates/beads

sandwich
competition
direct/indirect
inhibition

ECL Electro chemiluminescence

automate

high sensitivity,
accuracy,
broad dynamic range
low background
low volume of sample
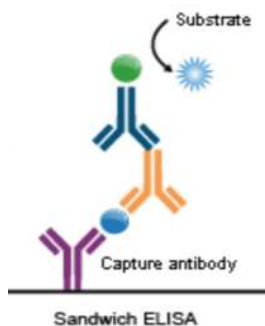
Method validation/qualification
commercial or in-house:
Fit-for-purpose approach
RUO / IUO / GCP GLP env

Reference interval for [BMK],
Optimize use of samples (pre-analytical)
Linearity, Parallelism
Calibration curve,
Selectivity
Specificity
Accuracy (deviation)
Precision
Sensitivity
Stability (short & long term)

100 to 200 samples per day

Spectramax M3 and i3x (Molecular Devices)

Meso QuickPlex SQ120 (Meso Scale Discovery)

Sandwich ELISA

ELISA

MSD-ECL

Biomarkers

LC-MSMS

Mass spectrometry   LC-MSMS   MRM/Single Plex

>1200 analytical methods developped in the lab (peptides & small molecules)

GHB (bioequivalence) FDA

Cortisol and hydrocortisol (clinical study BMK) ; FDA

Nicotine (bioequivalence) FDA

▪10 LC-MS/MS systems: API 4000 (3), API5500 (2), Shimadzu 8060 (3), API6500 (2)

▪HPLC systems with UV, fluorescence and diode array detection

▪Liquid scintillation counters (beta radiation)

▪On line HPLC with radiometric detector

Method validation/qualification
Fit-for-purpose approach
RUO / IUO / GCP GLP env

Linearity
Selectivity & Specificity
Carry-over
Matrix effect
Recovery (exctraction)
Accuracy & Precision
Timeof run impact
Stability
freeze and thaw cycles
Stability - bench top
Stability long term

60 to 80 runs per day

Biomarkers

Guidances

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Supporting DMPK from screening to registration

BEST FDA guidelines & Guidance for Industry

Biomarker
Qualification:
Evidentiary Framework
Guidance for Industry and FDA
Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Office of New Drugs at CDER-BiomarkerQualificationProgram@fda.hhs.gov , or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2018
Drug Development Tools

Bioanalytical Method
Validation
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)

May 2018
Biopharmaceutics

Bioanalytical Method Validation
05/21/18

CRITICAL PATH INSTITUTE

Points to Consider Document:
Scientific and Regulatory Considerations for the
Analytical Validation of Assays Used in the
Qualification of Biomarkers in Biological Matrices

June 11, 2019

Biomarker Assay Collaborative Evidentiary Considerations
Writing Group, Critical Path Institute (C-Path)

Steven P. Piccoli, GlaxoSmithKline and John Michael Sauer, Critical Path Institute

Contributing Authors:

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Commenters:

Candace Adamo, Pacific Biomarkers, Inc.; Abbas Bandukwala, U.S. FDA; Montserrat Carrasco-Triguero, Genentech; Lou Christodoulou, UCB; Anonymous, European Bioanalytical Forum; Swati Gupta, Allergan; Paula Katavolos, Genentech; Kellie Kelm, U.S. FDA; Dan Krainak, U.S. FDA; Adora Ndu, Biomarin; Corinne Petit-Frère, Roche; Hugo Vanderstichele, ADx NeuroSciences; Parya Nouri, Pfizer; Phillip Turfle, U.S. FDA; Yoshiro Saito, National Institute of Health Sciences; Sofia Stinchi, Merck; Yan Zhang, Bristol-Myers Squibb

Biomarker Assay Collaborative Evidentiary Considerations Writing Group   1

ICS › 11 › 11.100 › 11.100.10

ISO 18113-1:2009
**Dispositifs médicaux de diagnostic in vitro —
Informations fournies par le fabricant (étiquetage) —
Partie 1: Termes, définitions et exigences générales**

**GUIDE TECHNIQUE D'ACCREDITATION DE
VERIFICATION (PORTEE A) /
VALIDATION (PORTEE B) DES METHODES
EN BIOLOGIE MEDICALE**

Document SH GTA 04
Révision 01

Biomarkers

Biobanking

Discovery

Pre-clinical studies

Clinical studies

- Sample collection and storage procedures according to KOLs & literature guidelines (sample volume, DBS, -80°C)

- Samples tracking with Watson LIMS system

- Short turn around time for sample analysis & results sending

➢ Clinical Data Interchange Standards data (CDISC)

➢ FDA compliant study reports and/or customers' template

29

Quality Assurance

Supporting DMPK from screening to registration

Quality Assurance

- **6 FTE trained and dedicated Quality Assurance auditors**

- **33 years of GLP compliance - regularly inspected**

  - ANSM

  - ANSES

  - COFRAC

  - US FDA

- **Regular, customer audits**

- **Internal quality assurance audits:**

  - Study

  - Process

  - Facility

  - Supplier audits

Strengths | Values

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Supporting DMPK from screening to registration

Why our clients come back to us

- **Reactivity**
- **Flexibility**
- **Respect of timelines**
- **Quality**
- **Communication**

Why our clients like working with us

- **Experience**
- **Qualified work-force**
- **Customer focus**
- **Multi-disciplinary**
- **Low staff turnover**

Supporting DMPK from screening to registration

Supporting DMPK from screening to registration

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