

ADME assessment of contrast media



A French global R&D solution provider including services & products

- ▶ As of 1st July 2010, SPI-Bio, Biotec Centre, Ellipse Pharmaceuticals and IDPS merged to become one of the leading companies acting in the pharmaceutical R&D European market:

Bertin Pharma

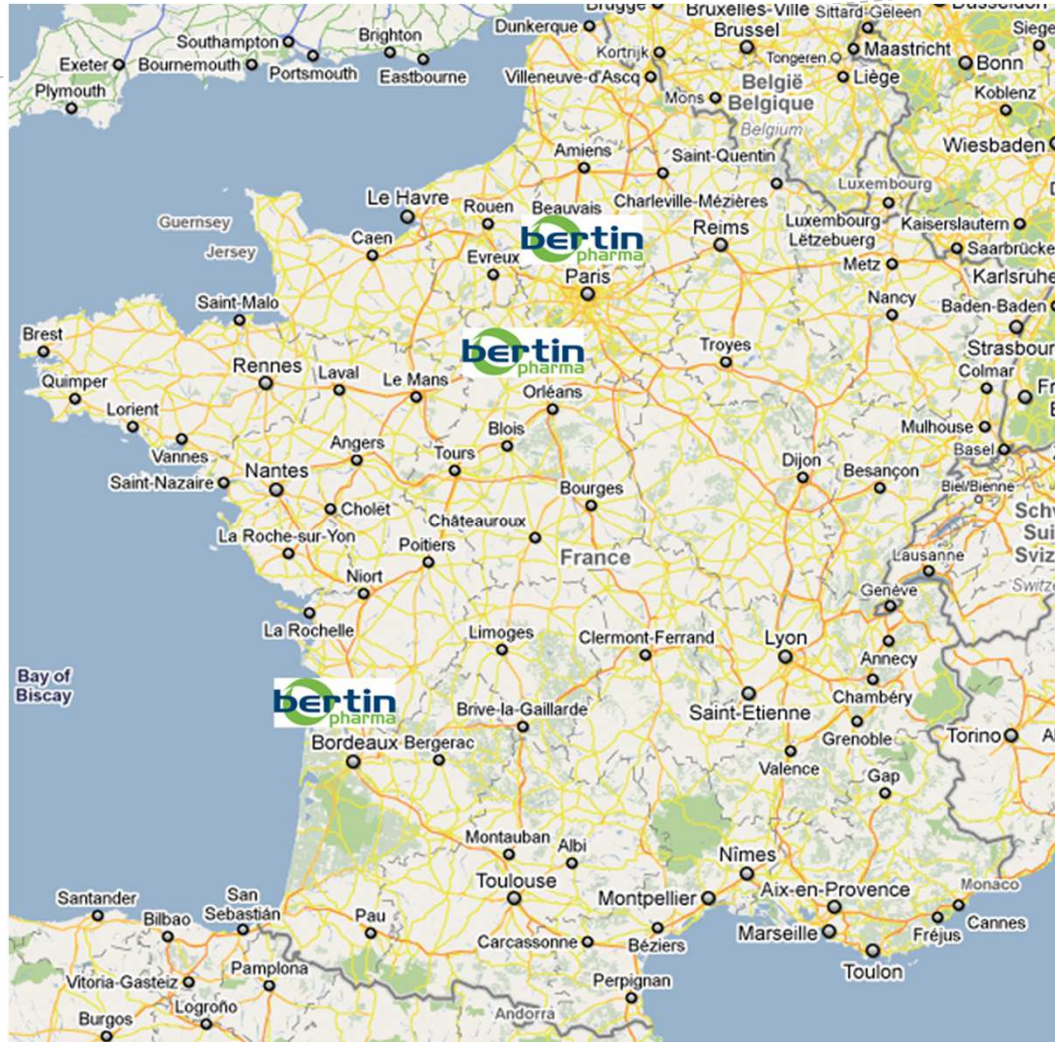
Bertin Pharma is a **global R & D solution provider** offering services, along with products, in the fields of pharmacy, biotechnologies, cosmetics and nutrition for both industries and academic research.

Bertin Pharma brings you expertise covering the whole drug development process including:

- ▶ Preclinical & Clinical studies
 - ▶ Pharmaceutical development & clinical supplies
 - ▶ Biosafety
-
- ▶ Including a focus on Biologics



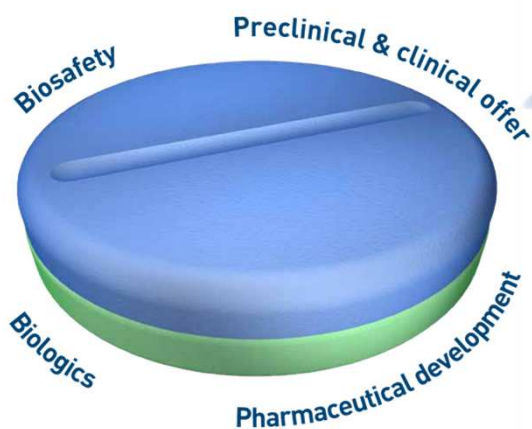
Bertin Pharma site facilities



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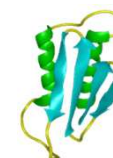
Pharmaceuticals development & clinical supplies:

- Pre-formulation & formulation (NCE, products obtained from biotechnologies and highly potent products),
- Industrial transfer,
- Manufacturing & packaging of clinical and commercial supplies,
- Quality control & dispatch of clinical supplies,
- Clinical supplies,
- Analytical development & stability studies according to the ICH, Regulatory affairs.



Preclinical & clinical studies:

- ADMET,
- Biotransformation,
- Biomarkers,
- Pharmacology



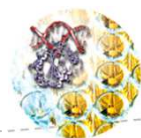
Biosafety

- *In vitro* & *in vivo* microbiological safety assessment toward HIV and non-conventional agent (prion)



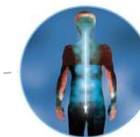
Biologics:

- Protein & HCP analysis,
- Immunogenicity,
- Immunomonitoring,
- Formulation





ADME applied to Contrast Media (1/4)



Contrast media consist in various range of products including:

- ▶ Radiographic contrast media (x-ray & computed tomography)
- ▶ Iodinated Contrast Media (angiography, gastrointestinal tract, urinary tract, etc.)
 - ▶ Divided in High-Osmolar agents (HOCM) & Low (incl. Iso)-osmolar (HOCM) agents used mainly for imaging studies split in 4 classes
 - ▷ HO ionic monomers
 - ▷ LO ionic dimers
 - ▷ LO non-ionic monomers
 - ▷ IO non-ionic dimers
 - ▶ Main Physico-chemistry properties: osmolality, ionicity, viscosity, iodine content

	FORMULA	MOLECULE	IODINE/MOL	CLASS
NON-IONIC	dimer		6/1	6
	monomer		3/1	3
IONIC	dimer		6/2	3
	monomer		3/2	1.5



ADME applied to Contrast Media (2/4)



▶ Common PK:

- ▷ Intravascular route (IV, IA, Intra-cavity, subarachnoid cavity)
- ▷ Not able to cross an intact BBB, placenta passage
- ▷ Excreted via glomerular filtration (if non renal insufficiency)
- ▷ Short half-life (70% in urine after 6 hours)
- ▷ No protein binding
- ▷ No cell penetration
- ▷ Poorly metabolised

▶ Barium Contrast Media (gastrointestinal tract)

- ▶ suspension of insoluble barium sulphate particles which are not absorbed from the gut
- ▶ Common PK:
 - ▷ Feces elimination



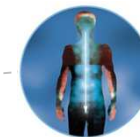
ADME applied to Contrast Media (3/4)



- ▶ **Paramagnetic Contrast Media** (Gadolinium & manganese chelates) & **Superparamagnetic Agent** (iron oxide agent) used mainly **for MRI**
 - ▶ Main Physico-chemistry properties: osmolality, viscosity, ionicity
 - ▶ 1st generation: Intravascular & interstitial space (BBB or the renal function)
 - ▷ Intravascular route
 - ▷ Excreted via glomerular filtration without secretion nor reabsorption
 - ▷ Negligible protein binding
 - ▷ Poorly metabolized
 - ▷ Short half-life (few hours max)
 - ▶ Liver-specific agents: gadolinium, manganese or iron oxide complex (hepatocytes or Kupffer cells)
 - ▷ Intravascular route
 - ▷ Liver accumulation of paramagnetic manganese is probably caused by metabolism of the parent compound
 - ▷ Possible involvement of organic anion transporting protein (OATP) for gadolinium chelates
 - ▷ Weak protein binding for hepatobiliary gadolinium chelates
 - ▷ Dual route (renal & hepatobiliary)



ADME applied to Contrast Media (4/4)



- ▶ Reticuloendothelial system (RES)-specific compounds: iron oxyde complex (accumulating in the macrophages of the lymph nodes, liver, spleen and lung)
 - ▷ Intravenous route
 - ▷ Detected in lysosomes where a metabolism takes place into a soluble form of iron which becomes part of the normal iron pool (e.g. ferritin, hemoglobin, etc.)
 - ▷ No uptake in hepatocytes

- ▶ Blood-pool agents: protein-binding or polymeric gadolinium complex, iron oxyde complex (angiography)
 - ▷ High protein binding to albumin
 - ▷ Excreted via glomerular filtration and to minor extent by hepatobiliary excretion
 - ▷ Unmetabolized

- ▶ Other: Atherosclerotic plaques, Tumor-specific agent
 - ▷ Long-circulating iron oxyde complex accumulating in monocytes & macrophages
 - ▷ Mab labeled with paramagnetic atoms or superparamagnetic nanoparticles

▶ Ultrasound Contrast Media

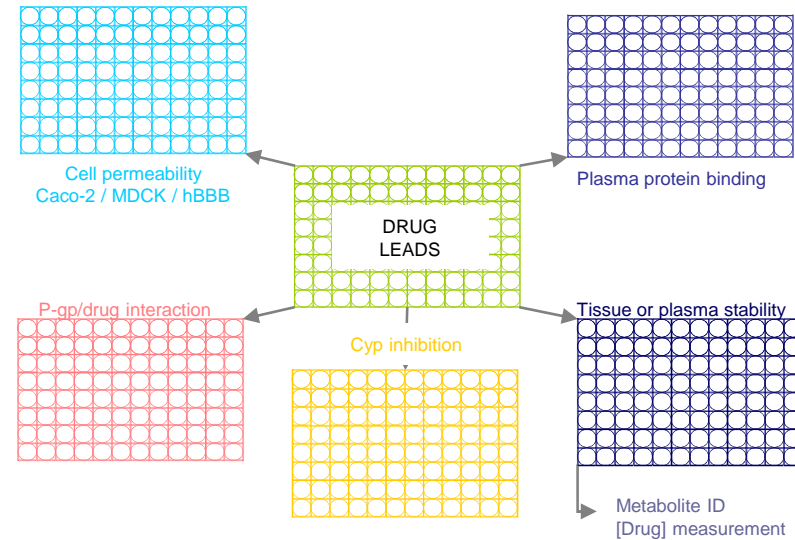


Contrast Media: Early ADME assessment



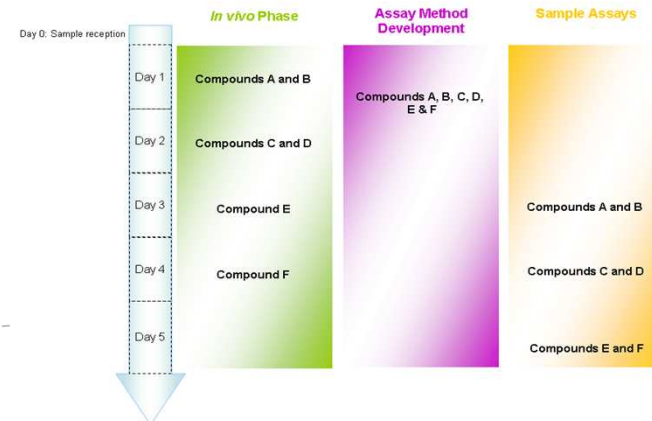
▶ Key issues *in vitro* ADME expertise in early development:

- ▶ BBB
- ▶ Protein binding
- ▶ ABC transporter binding



▶ Key issues *in vivo* ADME expertise in early development:

- ▶ PK profile applied to parenteral route
- ▶ Urine clearance

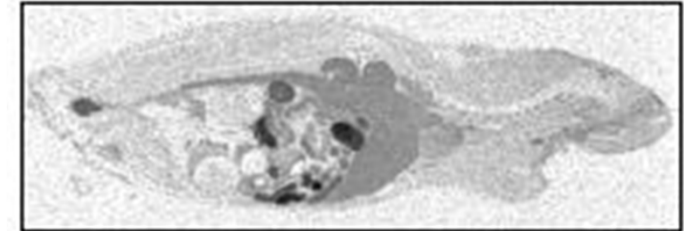




Contrast Media: animal PK

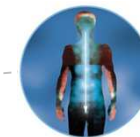


- ▶ **Plasma & urine pharmacokinetics**
- ▶ **Bioavailability** (not an issue)
- ▶ **Mass balance studies**
Liver specific agent, Barium sulphate
- ▶ **Quantitative Whole Body Autoradiography (QWBA)**
- ▶ **Tissue distribution**
Biliary (Gadolinium complexes)





Contrast Media: Human PK



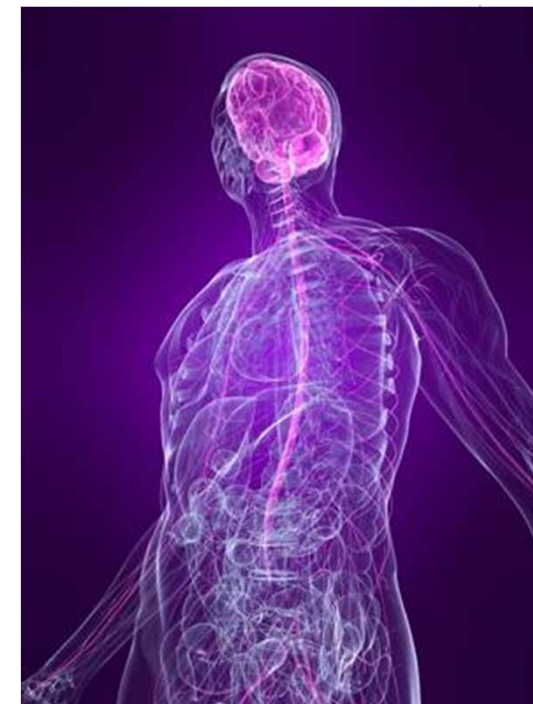
▶ Blood, plasma & urine kinetics

Balance of elimination

▶ Metabolic profile & structural elucidation (not a key issue)

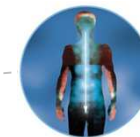
▶ Pharmacokinetics:

- ▶ Assessment of dose proportionality
- ▶ Assessment of multiple dose linearity (not an issue)
- ▶ Drug interaction studies
- ▶ Special populations (renal function impair)





Contrast Media: Drug/drug interaction



▶ ***In vitro/ex vivo* assessment:**

- ▶ **CYP based drug-drug interactions** (not a key issue)
- ▶ **Transporter based drug-drug interactions**
 - ▷ Cell permeability along with transporters study (Gadolinium chelates uptake by OATPs)

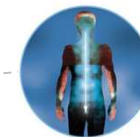
▶ **Pre-clinical Metabolic assessment** (not a key issue)

▶ ***In vivo* Drug/Drug Interaction linked to ADME Studies:**

- ▶ Possible reduction of renal function leading to interaction with drug mainly eliminated by renal route (Metformine leading to lactic acidosis)
- ▶ High osmolality contrast media may induce diuresis & natriuresis
- ▶ Nephrotoxic drugs (e.g. AINS) may potentially increase the renal effects of iodinated contrast media
- ▶ Diuretics may increased dehydration or electrolyte imbalance

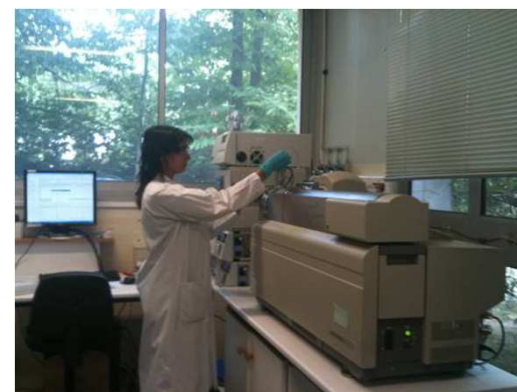


Bioanalysis



▶ Metal detection:

- ▶ AES (Atomic absorption spectrophotometry)
- ▶ ICP-AES (inductively coupled plasma Atomic absorption spectrophotometry)
- ▶ ICP-MS (inductively coupled plasma mass spectrometry)
- ▶ LC-FLS (Liquid chromatography-fluorescence)



▶ Complexe & derivatives:

- ▶ radiochemical detections of (125)I-labelled
- ▶ HPLC-ICP-AES
- ▶ LC-MS/MS





Conclusion



▶ Contrast media ADME studies should address:

- ▶ Vd, Cl ($t_{1/2}$), dose linearity
- ▶ Protein binding
- ▶ Route of elimination
- ▶ Drug/drug interaction

▶ Organe-specific target MRT (new contrast media)

▶ Not key issue: bioavailability, metabolism, accumulation (repeated doses)



Thank you for your attention!

For additional details, we remain at your entire service

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