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Rapid Late-Stage Lead Optimization

This service is designed to be a cost-effective and quick-turnaround solution to provide data within a few weeks. Pharmaron has combined our expertise in tritiation with our *in vivo*/*in vitro* drug metabolism capabilities to provide both tissue distribution and (optional) *in vitro* cross-species comparative metabolism data.

These data can play a vital role in making swift, affordable decisions around selecting and advancing the right lead candidate(s) prior to initiating IND-enabling toxicology studies. The *in vitro* species comparison information can assist with selection of toxicology species and obtaining an early detailed insight with into a compound's distribution and metabolism and help with translational sciences bridging non-clinical with clinical investigations.

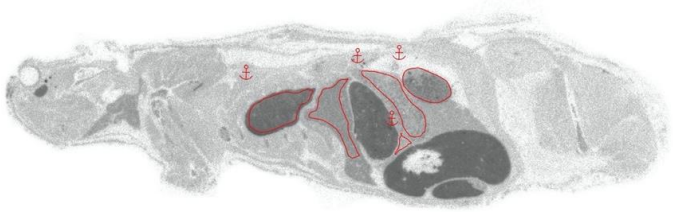
in vivo Tissue Distribution

- From ^{3}H radiolabelling to QWBA data in 2-3 weeks (for testing 5 compounds)
- Provides distribution data for ^{3}H radioactivity in up to 40 tissues in rodent
- Comparison of distribution in key tissues with basic quantification of blood:tissue ratios
- Key comparative target-distribution data for a panel e.g., 5 compounds in parallel

in vitro Metabolism

- Metabolism data in 2-6 weeks
- Quantitative comparison of metabolism in hepatocytes across species
- Identify formation of potential human-specific metabolites early
- Select most metabolically relevant toxicology species

Quantification of Radioactivity



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Laboratory Services

Chemistry, Manufacturing and Control

Clinical Development

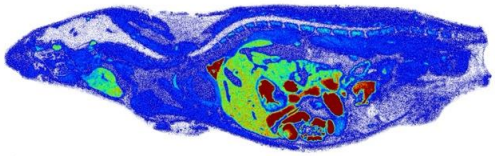
Biologics & CGT

Pharmaron is a global life science service provider that offers a broad spectrum of research, development and manufacturing service capabilities throughout the entire drug discovery, preclinical, clinical development and commercialization process.

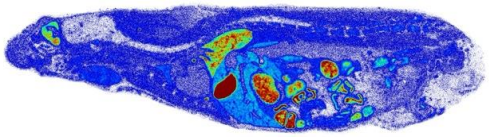
Rapid Late-Stage Lead Optimization

Autoradiographs

6 hours after ^{3}H-amlodypine administration



24 hours after ^{3}H-amlodypine administration



Week 1
Tritiation of Candidate Compound(s)

- Candidate compounds (e.g. a panel of 5 compounds) rapidly radiolabelled using catalyzed tritium exchange
- Compounds combined with a suitable catalyst, exposed to tritium gas and heated
- The tritium labelled compound produced is radio-diluted to a specific activity of approximately 1 mCi/mg with unlabelled compound
- The diluted tritium labelled compound is stored in ethanol (or other suitable solvent) until required (typical concentration 1 mCi/mL)

Week 2
QWBA by Novel Real-Time Digital Imaging

- Prepare simple [^{3}H]-Drug dose solutions e.g. oral in ultra-pure H_2O, IV in sterile isotonic saline
- Administer to male mice/rats by preferred dose route(s) e.g. oral, IV, subcutaneous
- Sacrifice one animal in each group per timepoint (select timepoints to show indicative rates of elimination and reveal any potential accumulation in target tissues)
- Rapidly freeze animals in hexane and solid CO_2, then process for whole body autoradiography and section animal(s) using the cryomicrotome
- Freeze-dry sections and analyze tissue distribution with novel digital 'real-time' autoradiography imaging system
- Blood:tissue ratio data and high resolution QWBA images of drug distribution available within 1 week of dose administration; full tissue quantitation available

Weeks 2-6
in vitro Cross-Species Metabolism

- Incubate ^{3}H test compounds with microsomes/hepatocytes (e.g. from mouse, rat, dog, minipig, NHP, human)
- Metabolite profiling by generic radio-HPLC methods to resolve and quantify metabolites and parent drug (data available within 2 weeks)
- Metabolite ID using HRMS with accurate mass (data available within 6 weeks)
- Overall timing dependent on extent and scope of analysis required

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