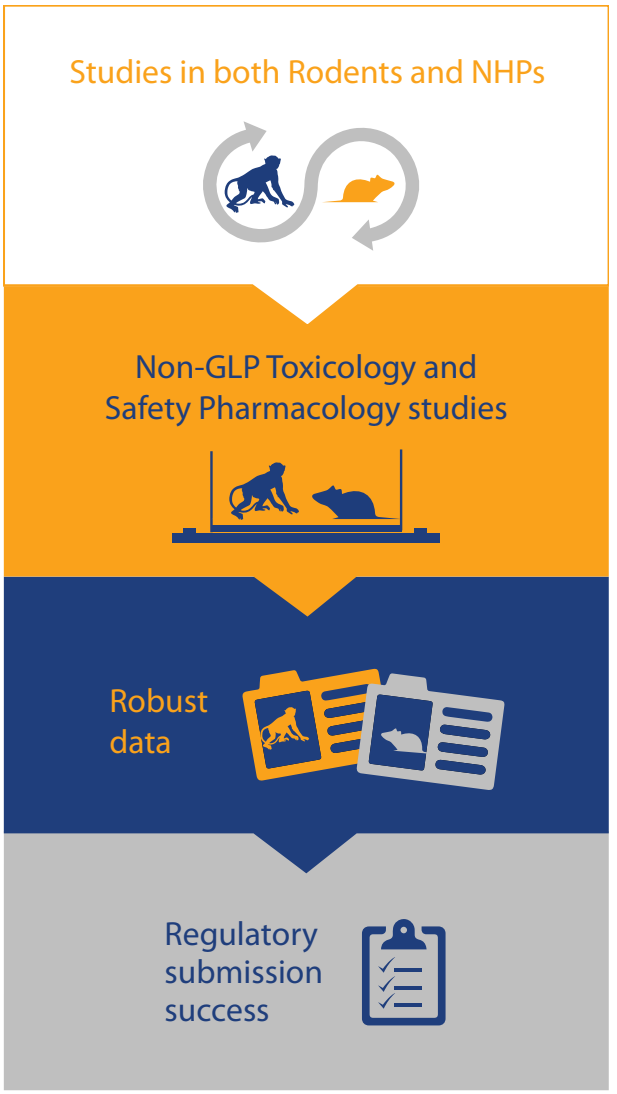
Non-GLP Toxicology and Safety Pharmacology Studies

CrownBio
CONNECTING SCIENCE TO PATIENTS

Submit your compounds with confidence using CrownBio Toxicology and Safety evaluation

Our range of Non-GLP Toxicology and Safety Pharmacology studies provide clients with maximum confidence for regulatory submissions.

- Comprehensive NHP Non-GLP Toxicology assay platform, for evaluating drug physiological and pathological effects, including spontaneously diabetic, dysmetabolic, and obese NHPs.
- Complemented by commercially available and proprietary rodent models of Type 2 diabetes and PKD.
- Safety Pharmacology rodent and NHP platforms, for standalone assessments or integrated toxicological profiling.
- Rapid study initiation for fast turnaround of robust results.
- Wealth of experience, providing client confidence with data and regulatory submissions.



+1.855.827.6968 | busdevcvmd@crownbio.com | www.crownbio.com

Non-GLP Toxicology and Safety Pharmacology Study Key Facts

CrownBio
CONNECTING SCIENCE TO PATIENTS

CrownBio provides a comprehensive Toxicology and Safety Pharmacology platform, across NHP and rodent models, to provide confidence in regulatory submission data

- Non-GLP Toxicology studies using healthy or dysmetabolic NHPs, with a range of common (i.v., i.m., s.c., p.o.) administration routes, as well as expertise such as intraperitoneal injection and intrathecal administration.
  - Comprehensive assessment program including blood, tissue, and organ collection, biopsy, and gross necropsy over a wide range of body systems, as well as a variety of assay and parameter collections.
- Non-GLP Toxicology rodent platform, including highly translatable models of Type 2 diabetes (ZDSD rat, FATZO mouse) and PKD (*jck* and *pcy* mice), alongside any commercially available rodent model.
  - With main study endpoints of necropsy, gross organ weight, and fixation for histology or rtPCR.
- Safety Pharmacology rodent and NHP studies, covering cardiovascular, hepatic, metabolic, and renal/urinary systems.
  - High definition data determined by continuous monitoring of cardiovascular and metabolic assessments, e.g. BP, HR, glucose levels.

Providing Maximum Confidence in Your Regulatory Submissions

CrownBio performs Non-GLP Toxicology and Safety Pharmacology studies for the evaluation of pharmaceutical and biotechnology products, providing robust, high quality data and allowing clients the maximum confidence with regulatory submissions. Non-GLP Toxicology studies can be performed across our collection of rodent models, as well as in our colonies of non-human primates (NHPs).

Non-GLP Toxicology Studies in NHPs

Using NHP models, CrownBio evaluates agents through a comprehensive assay platform, testing drug physiological and pathological effects. Studies can be rapidly initiated within 2 weeks (dependent on test article availability), with study duration optimized to fit individual client and project needs.

CrownBio provides healthy NHPs for toxicology studies, as well as our unique collections of spontaneously diabetic, dysmetabolic, and obese NHPs which can provide specific information if a client's test article(s) is targeted to treat one specific disease.

We can assess new agents delivered via several routes of administration:

- Intravenous injection or infusion
- Intramuscular injection
- Intraperitoneal injection
- Intrathecal administration
- Subcutaneous injection
- Oral routes – via diet or gavage

Following administration, our comprehensive assessments include tissue and organ collection, as well as a host of assays and parameter collections.

Tissue and Organ Collection	Assays and Parameter Collection
Blood/other bodily fluid collection	Clinical observation
Biopsy of liver, kidney, fat, muscle, skin etc. to fit client needs	Body weight, food/water consumption
Gross necropsy (sample number to fit client needs): • Morphology observation/weight • Organ/tissue collection • Organ/tissue fixation with 10% formalin • OCT cryopreservation • Liquid nitrogen (snap freezing for RNA) • Additional endpoints as required	Blood CBC, PBMC, cell sorting, and chemistry
	Blood pressure, ECG, glucose monitoring (including continuous monitoring)
	Hematology and bleeding tests
	Bone marrow slides and reading
	Urine assay
	Histology/IHC
	Slide section reading

We have experience in harvesting a wide range of organs across many organ categories, either pre- or post-exsanguination (detailed on the next page). Animals are perfused with heparinized saline sodium nitrite solution (99.8% physiological saline, 0.01% heparin, 0.2% 1% sodium nitrite) during approximately 5 to 10 minutes from the femoral vein, with all tissues collected within 30 minutes post perfusion.

Non-GLP Toxicology and Safety Pharmacology Study Factsheet

CrownBio
CONNECTING SCIENCE TO PATIENTS

System	NHP Organs Collected
Circulatory	Aorta, aortic arch, arteries (carotid, cephalic, coronary, femoral), heart (atrium, ventricle), spleen
Digestive	Colon, duodenum (distal to pylorus), esophagus, glands (parotid, salivary, sublingual), ileum, jejenum, liver (left/right lateral, median lobes), pancreas (body, head, tail), rectum, stomach (cardia, gastric body, pylorus), tongue
Endocrine organs	Adrenal gland, parathyroid, pituitary, thyroid
Immune/ hematopoietic	Bone marrow, lymph nodes (including mesenteric), peripheral blood smear, thymus, tonsil
Nervous	Brain stem, cerebellum, cerebrum, corpus callosum, hypothalamus, optic chiasma, sciatic nerve, spinal cord
Reproductive	Epididymis, mammary gland, ovary, oviduct, prostate, seminal vesicle, testis, uterus (including cervix, endometrium), vaginal duct
Respiratory	Bronchus, lung (anterior segment of superior lobe, parenchyma), trachea
Urinary	Bladder, kidney (medulla, cortex), ureter, urethra
Other	Eye (cornea, retina), omental adipose, skeletal muscle (quadriceps femoris), skin

Non-GLP Toxicology Studies in Rodent Models

CrownBio also provides a wide range of toxicity studies using rodent models. Assays can be performed in any commercially available rodent model, or in our proprietary highly translatable models of Type 2 diabetes (FATZO mouse, ZDSD rat) or PKD (*jck* and *pcy* mice, *PCK* rat).

Similar to Non-GLP Toxicology evaluation in NHP models, our main capabilities in rodents include:

- Necropsy
- Gross organ weights
- Fixation for histology or rtPCR
  - 10% buffered formalin
  - OCT cryopreservation
  - RNAlater®.

Safety Pharmacology Studies

As part of our General Toxicology Platform, we also provide Safety Pharmacology studies to assess the potential side effects of your new agents, either as standalone assessments, or embedded within our overall toxicological profiling.

Our comprehensive Safety Pharmacology evaluations in rodents and NHPs include the assessments shown below.

System	NHP Safety Studies	Rodent Safety Studies
Cardiovascular	BP, HR including continuous telemetry monitoring, ECG, cardiac function via noninvasive echocardiography	BP, HR including continuous telemetry monitoring, cardiac injury biomarker panel (MSD)
Hepatic	Echo evaluation of fatty liver (for long term study)	Blood chemistry, biomarker panel
Metabolic	Long-term continuous monitoring of blood or interstitial glucose via telemetry device	Long-term continuous monitoring of glucose via telemetry device, biomarker assessment (Std. ELISA and MSD)
Renal/Urinary	Renal function, blood chemistry, protein assays	Renal function, blood chemistry, kidney injury biomarker panel (MSD)

To provide high definition data, CrownBio can perform both cardiovascular and metabolic assessments via continuous telemetry monitoring. Blood pressure (BP) monitoring via radio telemetry is available for our NHP and rodent models. Our rodent system is fully enclosed within the test animal, with the monitor usually implanted in the abdominal aorta and the battery localized in the abdominal cavity. The animal cage is placed on a receiver, allowing continuous BP measurement as required, with experiments performed over several months if needed. Experimental readouts include mean arterial pressure (MAP), systolic and diastolic pressures, and heart rate (HR).

Continuous glucose monitoring is available for both our rodent and NHP models using DSI technology, allowing continuous biochemical and physiological evaluation post-agent administration. In rodents, the technique is available for rat models, and is currently undergoing final validation in mice. The telemetry device probe is implanted into the aorta of the animal, and is coated with glucose oxidase to monitor glucose concentration. The device can be used for approximately four week studies (limited only by the probe lifetime which is based on the amount of glucose oxidase which can be loaded).

In NHP models we use technology such as the DSI HD-XG transmitter device. The glucose sensor is implanted in the femoral artery, with the device body implanted subcutaneously nearby. A small repeater is carried in the monkey jacket for remote signal collection outside of the cage. Blood glucose can then be monitored wirelessly and recorded continuously for more than 6 weeks, to provide high quality continuous data.