Methodologies for Collecting Clinical Biomarker Data in Laboratory Animals

Overview

- **ICH S7 Guideline Objectives**
- **Safety Pharmacology**
  - "Core Battery" Safety Studies
    - Cardiovascular Pharmacology (addressed previously)
    - Neurobehavioral Pharmacology
      - *Functional Observational Battery, Irwin test*
    - Respiratory Pharmacology
  - "Supplementary" Studies
- **Possible Alternatives and Reduction**

ICH = International Conference on Harmonisation

ICH Guideline Objectives

1. Identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety;
2. Evaluate adverse pharmacodynamic and/or pathophysiological effects of a substance observed in toxicology and/or clinical studies; and
3. Investigate the mechanism(s) of the adverse pharmacodynamic effects observed and/or suspected.

ICH S7 section 2.1

Core Battery

2.7 The purpose of the safety pharmacology core battery is to investigate the effect of the test substance on vital functions.

2.7.1 Central Nervous System

2.7.2 Cardiovascular System (previously discussed)

2.7.3 Respiratory System

ICH S7 section 2.7

Supplementary Battery (not discussed)

2.8.2 Supplemental studies are meant to evaluate potential adverse pharmacodynamic effects on organ system function not addressed by the core battery or repeated dose toxicity studies when there is a cause for concern.

2.8.2.1 Renal / Urinary System

2.8.2.2 Autonomic Nervous System

2.8.2.3 Gastrointestinal System

2.8.2.4 Other Organ Systems

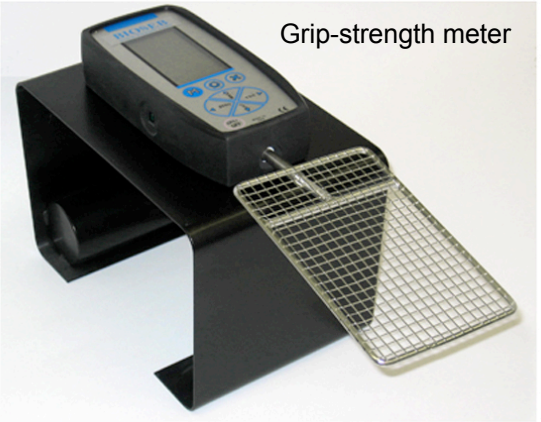
- *e.g., dependency potential, immune function, skeletal muscle, endocrine function*

2.7.1. Central Nervous System

- **Tier 1: Functional Observation Battery (*aka* FOB, Irwin test)**
  - Approximately 30 endpoints
    - including motor activity, behavioral changes, coordination, sensory-motor reflexes, and body temperature
  - Home Cage Observations (~2 min)
    - *Passive observations of the rat in its Home Cage*
  - Handling Observations (~2 min)
    - *Observations made while removing (=Handling) the rat from its Home Cage*
  - Open-Field Observations (~3 min)
    - *Observations made while the rat explores a novel open area*
  - Reflexes and Physiological Measurements (~5 min)
    - *Objectives measurements of body temp., hind-/fore-limb grip strength, landing foot splay, etc.*
- **Tier 2: Follow up studies based upon FOB findings**
  - Motor activity, neuromuscular function/coordination, reflexes, etc.

Typical Central Nervous System Study Design

- Adult male rats (unless females requested)
- Control, Low, Mid, High dose levels (N= 6-10 rats/group)
- Single dose administration by expected clinical route (e.g. oral)
- Procedure: Rats are treated and then evaluated at one or more times post dose such as Tmax, 24 hr
- Rats are euthanized at the conclusion of the observation period with no further analysis



2.7.3 Respiratory System

- **Tier 1:** Respiratory assessment in plethysmograph-restrained rats
  - Respiratory Rate (breaths per minute); breathing frequency
  - Tidal Volume (ml per breath); depth of breathing
  - Minute Volume (ml per minute); airflow during a fixed interval
- **Tier 2**: Follow up studies based upon any findings
  - Bronchospasm, respiratory depression, ventilatory disorders, etc.
  - Centrally and/or peripherally mediated?

Typical Respiratory/Pulmonary System Study Design

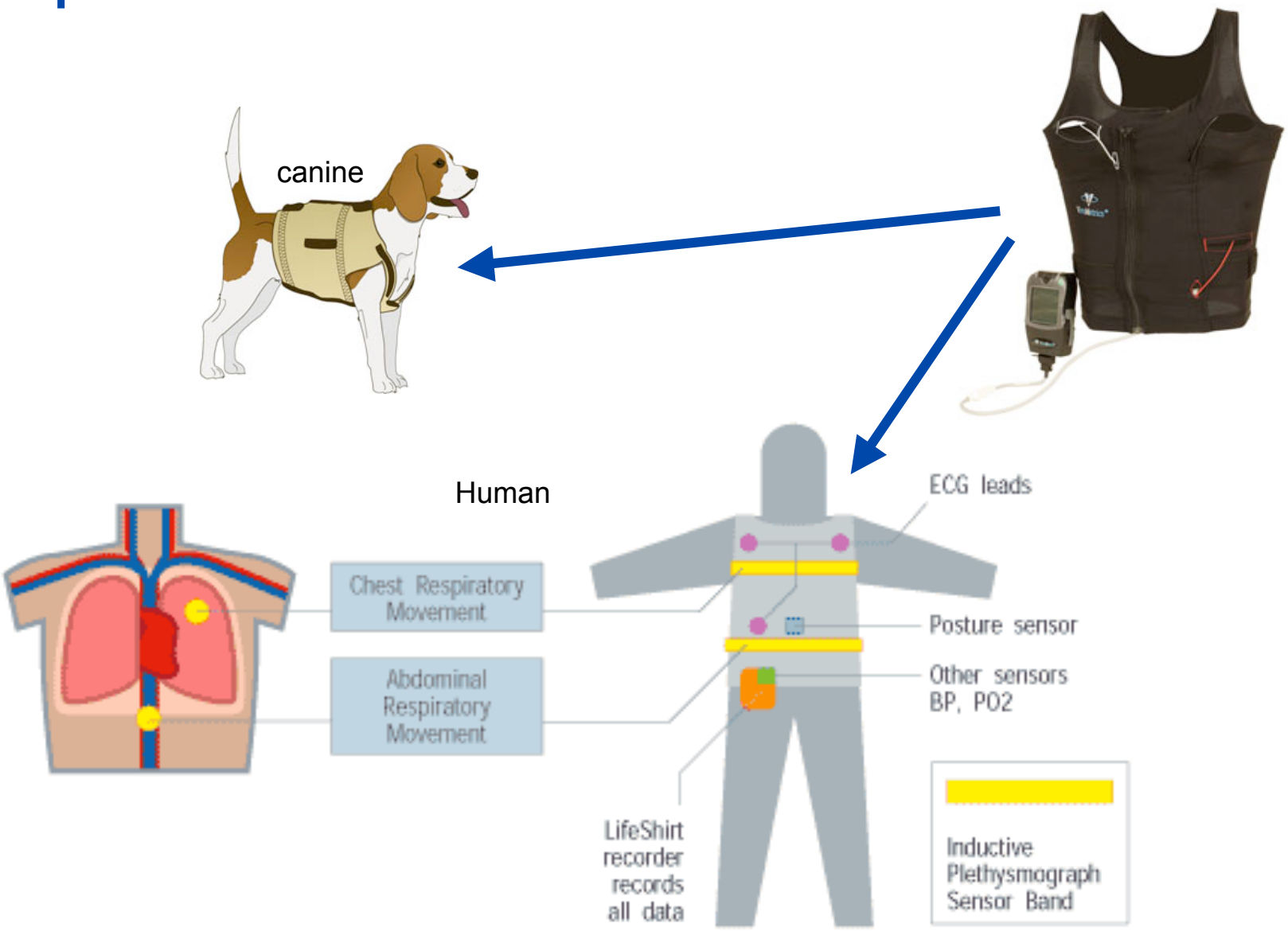
- Adult male rats (unless female requested)
- Control, Low, Mid, High dose levels (N= 8-10 rats/group)
- Single dose administration by expected clinical route
- Procedure: Pre-test rats are acclimated to a plethysmograph chamber. On the day of dosing, pre-treatment baseline data are collected, followed by treatment and continuous data collection for at least 4 hours.

Unrestrained rodent whole-body chambers

Possible Alternatives and/or Reductions

- **Include CNS in GLP definitive study**
  - Conduct FOB on Day 1 or 28 at Tmax of compound
- **Include respiratory and cardio function in GLP definitive study**
  - New sensor technologies for external non-invasive measurements of heart rate (including posture and activity), electrocardiogram (ECG), electroencephalogram (EEG), electrooculogram (EOG), periodic leg movement, body temperature, respiratory tidal volume, end tidal CO2, blood oxygen saturation, blood pressure, cough/bronchial spasm, polysomnography (sleep)
  - Monitoring sensors can be worn continuously (similar as in ambulatory patients)
- **Screen compounds against receptor and pharmacology panel(s)**
  - Kinases, G-coupled protein receptors (GCPRs), nuclear receptors, neurotransmitter receptors, ion channels, enzymes, etc.
- **Expanded evaluation of biological fluids/tissue**
  - Emphasis on potential clinical biomarker tissues (blood, urine, buccal cells, etc)
  - Include cardiac troponins, CK-myoglobin, C-reactive protein (CRP), brain natriutic peptide (BNP) in GLP definitive studies

Example: VivoMetrics LifeShirt®



Definitive IND-Directed Repeated Dose Safety and Toxicity

- **Rodent and non rodent models**
- **4 Dose Groups + Recovery: Control (vehicle), Test Article (low, mid, high)**
- **Dosing by intended route and approximate frequency**
- **Standard Endpoints:**
  - Clinical Observations, Body Weight, Food Consumption, Urinalysis, Ophthalmology, Clinical pathology (clinical chemistry, hematology, coagulation)
- **Safety Pharmacology:**
  - **CNS - rodent (canine/primate also possible)**
  - **Cardio and Respiratory - canine/primate**
- **Toxicokinetics (TK)**
- **Histopathology (all tissues)**
- **Identify Maximum Tolerated Dose (MTD) and No Observable Adverse Effect Level (NOAEL)**

Helpful Links and References

- **U.S. Code of Federal Regulations**

  http://www.gpoaccess.gov/cfr/index.html

  – 40CFR 798.6050 Functional Observational Battery

- **FDA Guidance documents**

  http://www.fda.gov/cder/guidance/index.htm

- **ICH Guidelines**

  http://www.ich.org/cache/compo/276-254-1.html

  GoTo: Publications ➔ Guidelines ➔ Safety

- **Continuous vital sign monitoring**

  http://www.vivometrics.com/