

Applied Research/Testing of Novel and Proprietary Compounds:

**Controversies and challenges faced by
academic animal care committees**



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Overview



- 1. Defining the Issues**
- 2. Aspects of Compound Testing**
- 3. Scientific Validity and Ethics**
- 4. Recommendations**

1. Defining the Issues:

What Constitutes Animal Use in Applied Research/Testing?



- **Industry testing in Academia**

Direct industry activity in academia

Academics contracted to test novel compounds

- **Academic Development of new compounds**

Determination of biological activity in vivo

Goal to develop clinically relevant compounds

1. Defining the Issues:

Scientific Merit



● **Scientific Merit of Applied Research***

Responsibility of the research administration of institution to ensure that all (basic or applied) research in which animals will be used undergoes scientific peer-review before consideration of the corresponding animal use protocol by Local Animal Care Committee (LACC)

● **Regulatory Merit of Regulatory Testing***

Responsibility of institution to ensure that study director, Regulatory Affairs official or other institutional representative has ascertained that data obtained will be acceptable to regulatory authorities (Health Canada)

However, Regulatory Testing requires all later stage preclinical testing to be done in accredited GLP (Good Laboratory Practice) facilities utilizing GMP (Good Manufacturing Practice) prepared compounds**

**CCAC policy statement for: senior administrators responsible for animal care and use programs. (2008)*

***Health Canada: Non-Clinical Laboratory Study data supporting drug product applications and submissions: adherence To Good Laboratory Practice. (2010)*

1. Defining the Issues:

Increased Interaction of LACCs and Animal Testing



- **Cost and Funding**

- decreased private funding of biotech
 - increased academic vivaria costs

- **Fewer Contract Research Organizations (CRO)**

- more preliminary investigations done at universities

- **Increased Patent Protection Costs**

- IP protection costs reduce research budget

- **Increased Number of New Drug Entities**

- genomic, proteomic methods increase number of bioactive compound candidates



Result: LACCs are under increasing pressure to consider AUPs associated with animal testing of novel compounds

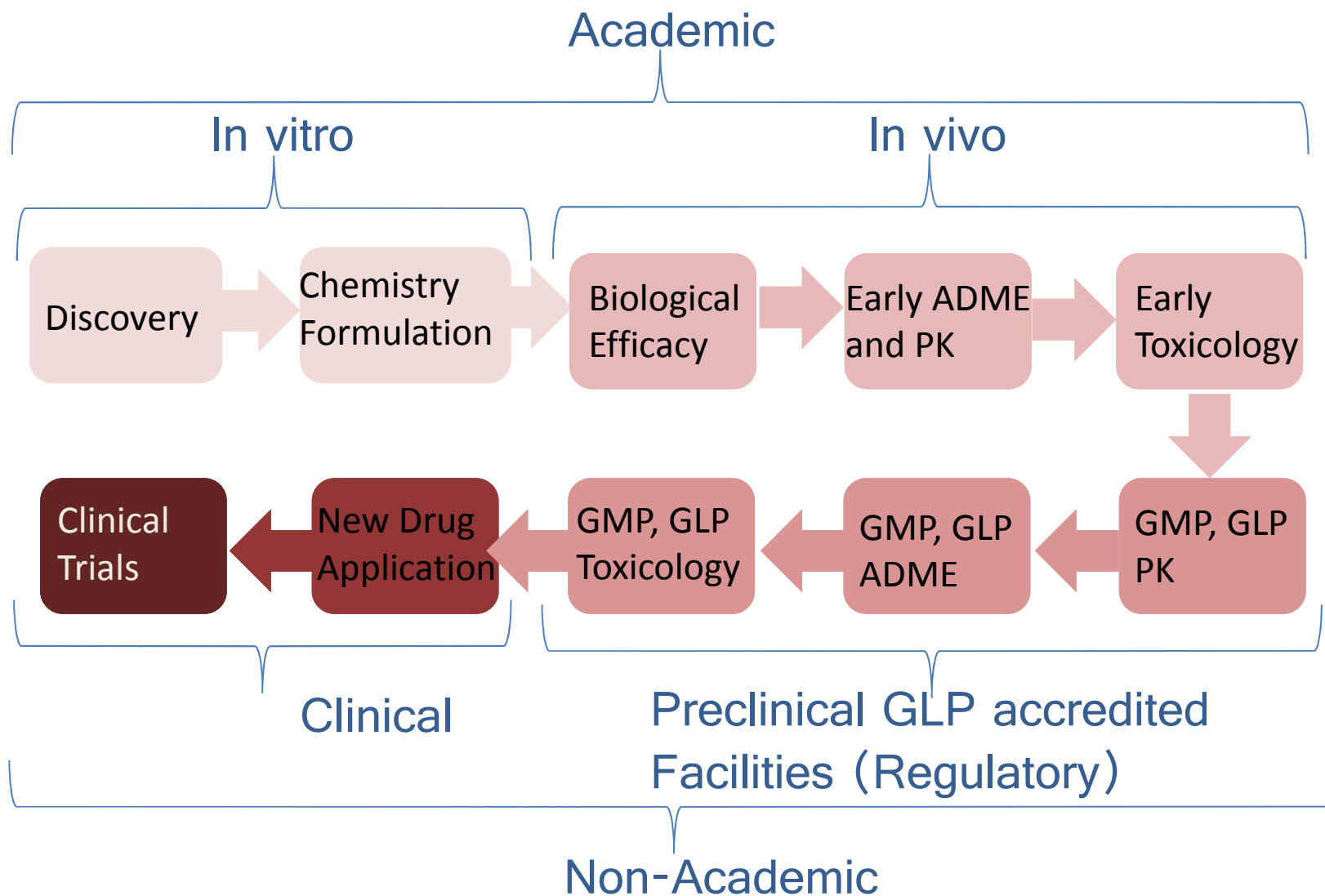
2. Aspects of Compound Testing Overview



- **Chemistry and Formulation**
- **Administration Route**
- **Dose and dose regimen**
- **Pharmacokinetics (PK)**
- **Absorption, distribution, metabolism, excretion (ADME) characteristics**
- **Toxicology**

2. Aspects of Compound Testing

Road to Development: Discovery to Clinical Testing



2. Aspects of Compound Testing

Chemistry and Formulation

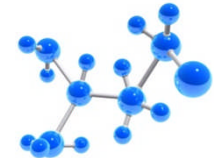


Physical Attributes

structure type, mass, solubility



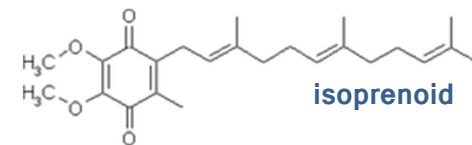
Protein



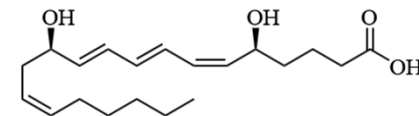
Peptide

Excipients

Additions to increase solubility and biological activity (eg. DMSO, buffers, cyclodextrin, etc.)



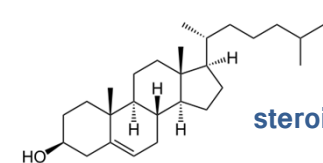
isoprenoid



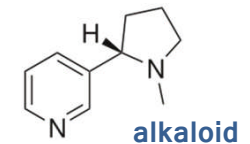
eicosanoid

Endogenous and Exogenous Compounds

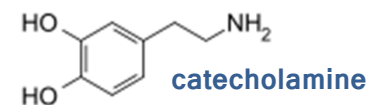
Natural or alien to the testing species



steroid



alkaloid



catecholamine

2. Aspects of Compound Testing

Administration Route



- **Intracranioventricular (ICV)**
- **Intravenous (IV)**
- **Subcutaneous (SC)**
- **Intraperitoneal**
- **Nasal (drip and inhalation)**
- **Orbital**
- **Other**

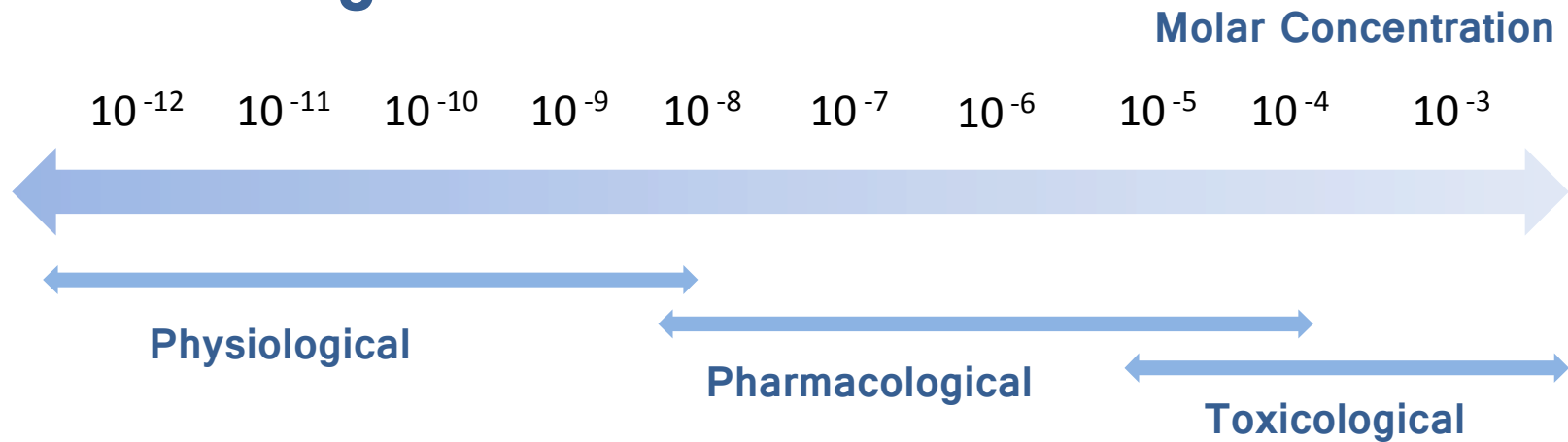
Depending on the compound some routes may be more effective than others.

2. Aspects of Compound Testing

Dose and Dose Regimen



Dose Range



Dose Regimen

how many administrations over time period: will depend on:
route of administration and
residency time in tissues (PK, ADME)

2. Aspects of Compound Testing Pharmacokinetics



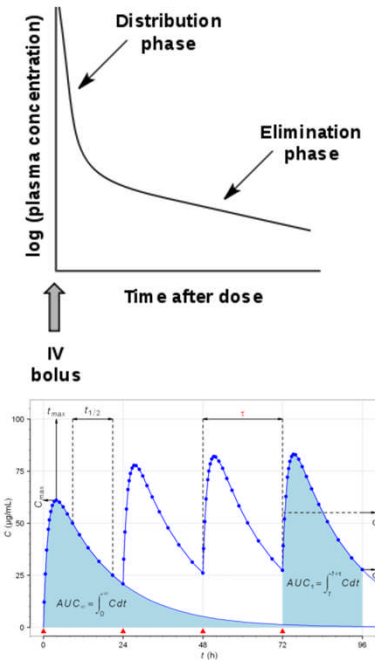
Fate of the substances administered to an animal
How long can a particular compound be measured
in a particular tissue?

Plasma Concentration Curves

ELISA, RIA, Mass spectrometry

Compartmental Analyses

determination of PK attributes in different biological compartments



2. Aspects of Compound Testing ADME



● Absorption

Dependent on administration and movement across epithelial tissues into the bloodstream.

● Distribution

Movement into various tissues and particularly across Blood-Organ barrier sites (e.g. blood-brain barrier).

● Metabolism

Metabolic breakdown of administered compound. Though some compounds are non-toxic, per se, their secondary metabolites may be toxic.

● Excretion

How much is excreted or eliminated? This information is required to determine how much is stored in the tissues. Essential for determining repeated dose regimens.

2. Aspects of Compound Testing Toxicology



- **Biomarker Studies**

Effect of varying concentrations on molecular indicators

- **Imaging Studies**

PET, NMR, EEG, ECG based studies*

- **Behavioural Studies**

Grooming, exploratory activity, memory, anxiety, learning, depression, social interaction

- **Morphological Studies**

animal appearance and mass, organ morphology and mass, histology of tissues

- **Lethality Studies**

50% Lethality (LD50)

*PET: positron emission tomography, NMR: nuclear magnetic resonance, EEG: electroencephalography, ECG: electrocardiography

3. Scientific Validity and Ethics



LACC is not tasked to evaluate the research

- Acceptance of peer review by granting agencies or by internal or external independent, expert review of research program or project
- Research AUPs typically detail the proposed execution of the animal-based part of a research program or project

The LACC's task is to evaluate the AUP design and proposed animal-based methods with respect to whether they are appropriate and incorporate the Three Rs, given the expected outcomes.

For new compounds, no published literature may exist: This is a particular challenge for LACCs

3. Ethical and scientific considerations for the institution and its LACC



- Should an LACC that has no expertise in pharmacological or toxicological testing protocols consider such protocols?
- Should an institution and its LACC consider toxicology testing in general?
- Should an academic (public) institution be engaged in proprietary research?
- Should public funding be used to underwrite private research?
- Should investor-driven research be allowed to underwrite public research?

3. Ethical and scientific considerations for the institution and its LACC



- **Each LACC and UACC will need to consider ethical issues**
Will reflect philosophical position of committee and economic reality
- **UACC and LACC will not necessarily have control on external organizations utilizing University facilities**
- **Problem areas may include pain, neuro/muscular degeneration, lethality testing and chemical pathology AUPs**
- **Depending on the expertise of the committee, there will be varying amounts of comfort/discomfort with associated AUPs**

3. Concerns associated with applied research/testing protocols



- Confidentiality Issues
- Processing Times
- Methods may not be those considered most acceptable by the CCAC
- Animal numbers in AUP may not be consistent with standard statistical methods applied in basic research

4. Recommendations

Use of Proprietary Compounds



For AUPs associated with Non-Academic Peer-Reviewed Grants:

Essential: Independent, expert peer review, under the responsibility of the research administration, so that there are no conflict of interests for the LACC*

If AUP requires testing of proprietary compounds,

Recommended:

- A) University Peer-Review committee can include experts on drug testing
- B) If a particular LACC has received most or all of such applications, then a subcommittee should be considered to oversee such studies.

*CCAC Policy Statement for: Senior Administrators responsible for Animal care and use programs

4. Recommendations

Use of Proprietary Compounds



Subcommittee on Proprietary Compound Testing Requirements

Expertise to Include:

1. chemistry and metabolism of compounds
2. methodology of regulatory testing methods
3. familiarity with Health Canada regulations
4. Internal or external members

Required to be Submitted to LACC as an addendum to AUP:

1. Chemical (IUPAC*) and Common name of compound
2. Chemical Class
3. Molecular Mass (kDa)
4. Summary of PK, ADME and Toxicology data
5. Dosage and administration regimen

*IUPAC: International Union of Applied and Pure Chemistry