

Infusion Technology Organization - ITO

Development and implementation
of a new access button used
in the rat self-administration design

September 15, 2011

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- Introduction to abuse potential/liability
- Nonclinical drug abuse liability testing
- The self-administration model:
 - technical requirements
 - development of the VAB
 - how did we move on
 - implementation of the VAB in the SA model
 - choice of catheters in the SA model

Introduction to Abuse Potential/Liability

Definition

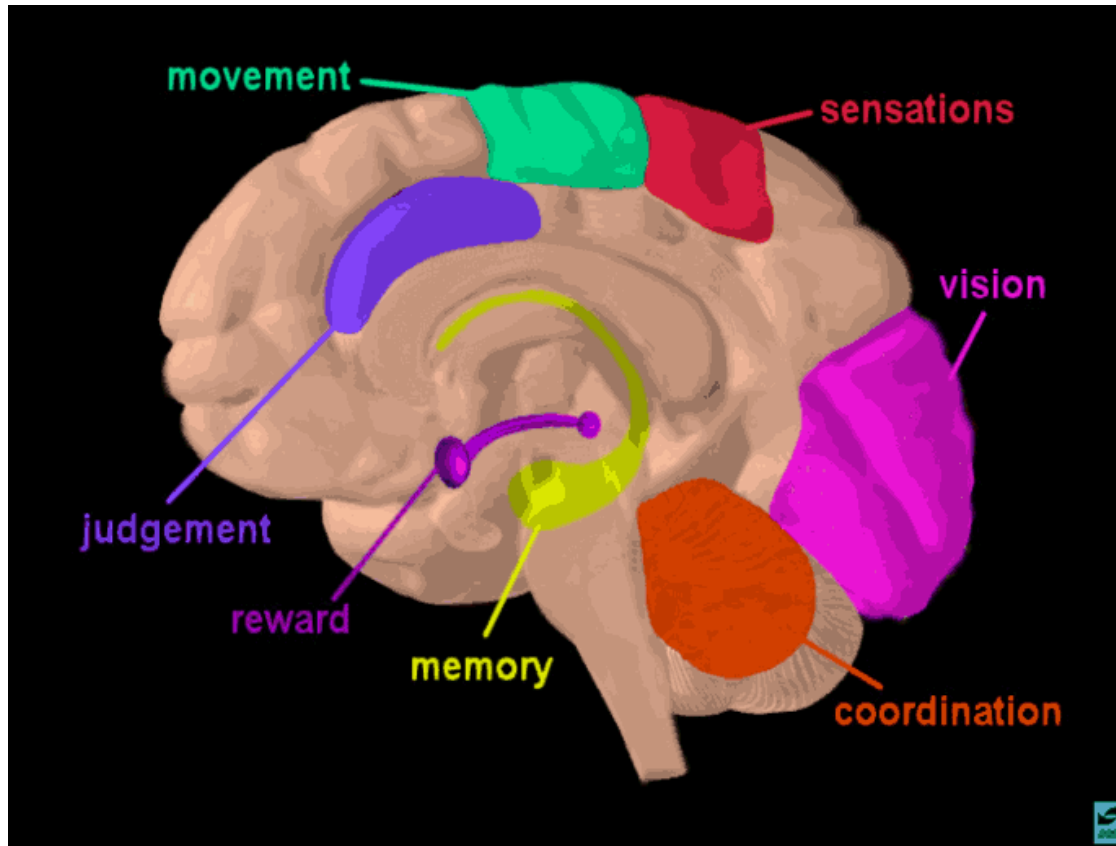
Abuse potential refers to a drug that is used in nonmedical situations, repeatedly or even sporadically for the positive psychoactive effects it produces (US).

Abuse liability refers to the likelihood that a drug product could be subject to user-initiated, non-therapeutic self-administration (Canada).

Dependence potential of an active substance is the propensity of an active substance, as a consequence of its pharmacological effects on physiological or psychological functions, to give rise to a need for repeated doses of the active substance to “feel good” or to avoid “feeling bad” (Europe)

Introduction to Abuse Potential/Liability

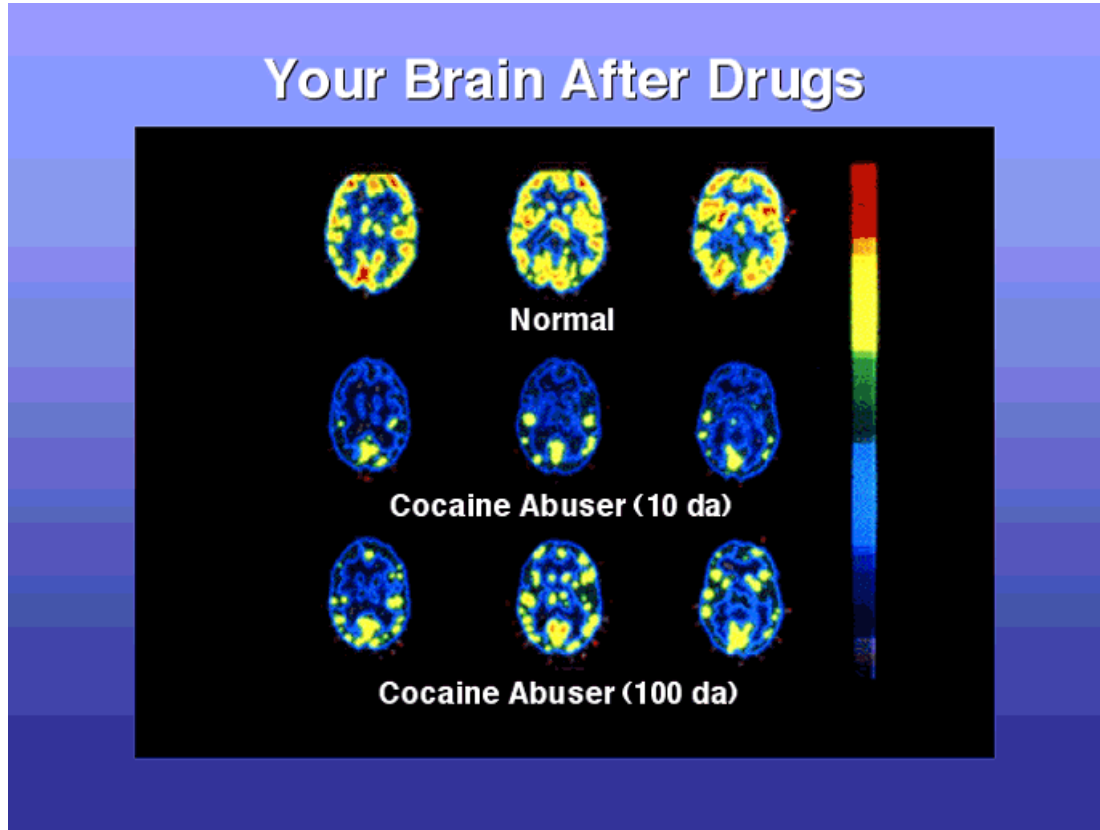
Mesoaccumbens dopaminergic system: important modulator



Examples of neurotransmitter systems of interest include the following:

- Dopamine
- Norepinephrine
- Serotonin
- Gamma-aminobutyric acid (GABA)
- Acetylcholine
- Opioid
- N-methyl-D-aspartate (NMDA)
- Cannabinoid

- Importance of avoiding drug abuse



Non-clinical drug abuse liability testing



The life of a lab rat

Non-clinical drug abuse liability testing

Guidance documents

EM(E)A: European Medicines Agency

EMEA/CHMP/SWP/94227/2004:

Guideline on the non-clinical investigation of the dependence potential of medicinal products (23 maart 2006)

ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICH M3 (R2): Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (11 Juni 2009)

FDA Guidance for Industry

Assessment of Abuse Potential of Drugs (26 Jan 2010)

Non-clinical drug abuse liability testing

Current regulatory guidelines

What products?

All new CNS-active medicinal products

- regardless of therapeutic indication
- metabolites which enter the brain
 - at relevant concentrations
 - that interact as central targets

Non-clinical drug abuse liability testing

Two-tiered approach

First tier: Pharmacology

Second tier: Behavioural pharmacology studies

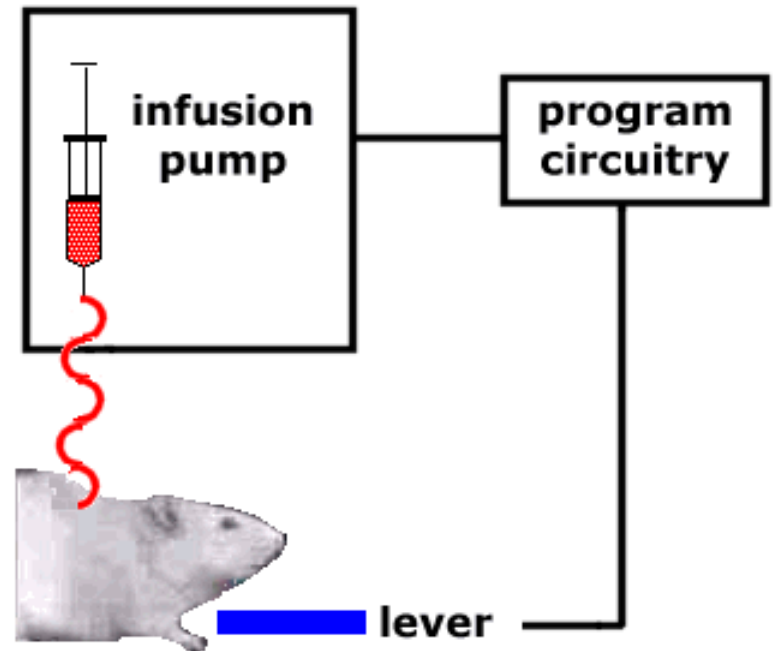
- | | |
|---------------------------------|--|
| 1) Withdrawal | physical dependence |
| 2) Conditioned Place Preference | conditioning, rewarding, reinforcing effects |
| 3) Drug Discrimination Learning | drug profiling |
| 4) Self-Administration | reinforcing effects |

Non-clinical drug abuse liability testing

IV self-administration

- animal model of human drug-taking behaviour
- experimental procedure for studying the reinforcing properties of drugs

Animals press a lever to obtain a drug or saline (self-administration).



http://www.addictionscience.net-rat_ivsa.mpg.url

Non-clinical drug abuse liability testing

IV self-administration (IVSA)

Procedure:

- a) Laboratory animals: surgically prepared with IV jugular catheters that permit automated drug injections.
- b) training of the animals to press a lever to self-inject various known reinforcing drugs (i.e. Cocaine, amphetamine,...).
- c) example study outline (per dose group):
 - Training (non-GLP): minimum 6 weeks
 - lever press
 - training psycho-active drug versus saline

GLP study: minimum 6 weeks

Phase 1 - Phase 2 - Phase 3 - Phase 4 - Phase 5 - TK
cocaine - saline - cocaine - TA - cocaine - TA

Non-clinical drug abuse liability testing

IV self-administration

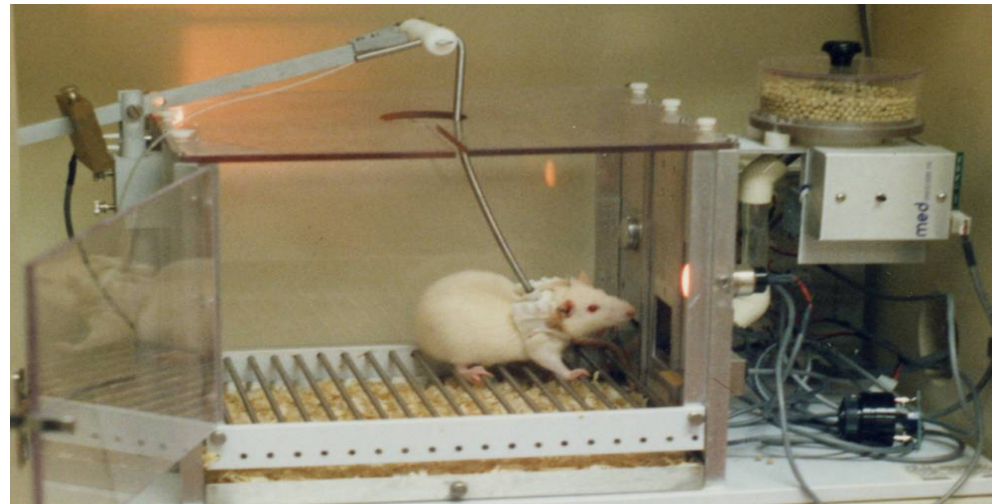
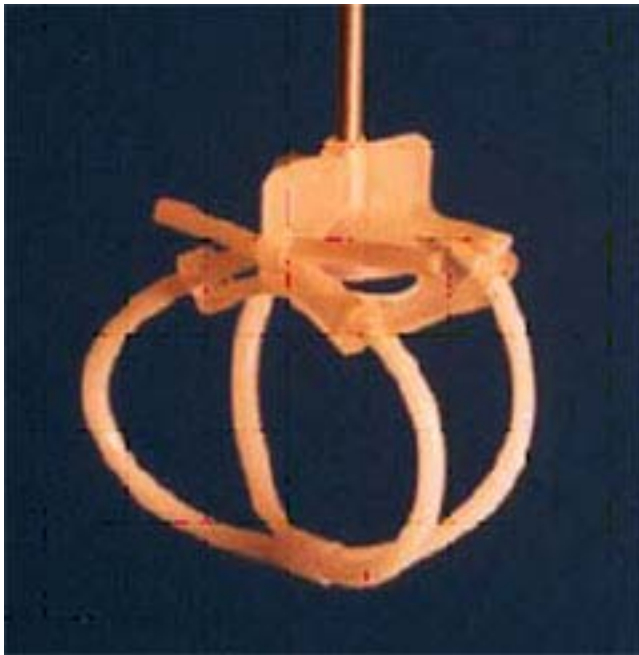
Technical requirements:

- System must be designed for long-term use
- System must be comfortable to the animal (i.e. rat)
- System includes:
 - internal catheter
 - **fixing medium:** - **harness**
 - **vascular access button**
 - swivel/tethering

Non-clinical drug abuse liability testing IV self-administration

Technical requirements:

- fixing medium:
- harness: - not very comfortable
- easy to bite through
- not in favour for use in SA model



Non-clinical drug abuse liability testing

IV self-administration

Technical requirements:

fixing medium:

- Existing vascular access buttons (VABs) on the market:
 - not comfortable to the rat: too big, heavy, limiting movements
 - no ideal type available for use in SA model (long-term)
(large tops, heavy material, ...)
 - some universities/companies construct VAB themselves
(not to be used as a standard within a GLP environment)



Need for a commercial system:

- to be used in long-term studies
- comfortable to the rat
- to be used in a GLP environment

Non-clinical drug abuse liability testing

IV self-administration

Technical requirements

-Instech Solomon and Drug Safety Sciences (DSSc) at Janssen Research & Development, Beerse, Belgium:

close collaboration to develop a prototype of a vascular access button for use in (long-term) SA studies

- no use of harness
- comfortable to the rat

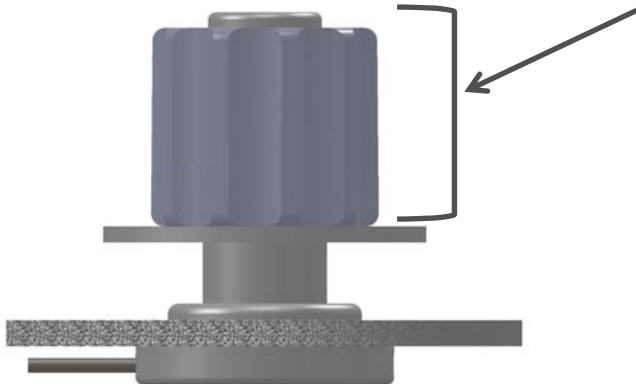
Non-clinical drug abuse liability testing

IV self-administration

How did we move on

-Problem solving:

- top VAB (tether connection) was reduced in height
(from 2.7 cm to 1.2 cm): more comfortable to the rat



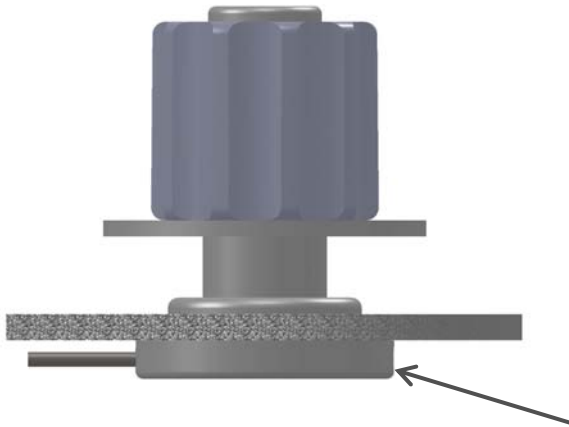
Non-clinical drug abuse liability testing

IV self-administration

How did we move on:

-Problem solving:

- a self sealing septum was applied
- easy for flushing procedures
- easy to connect with the tether



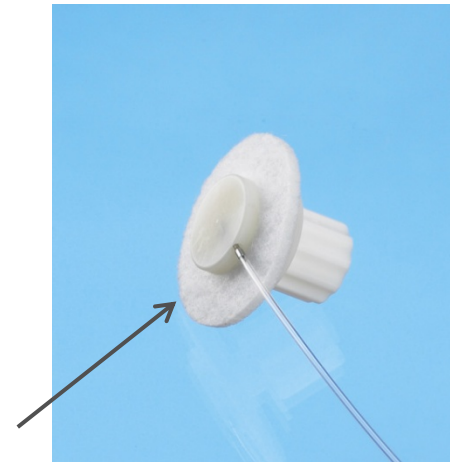
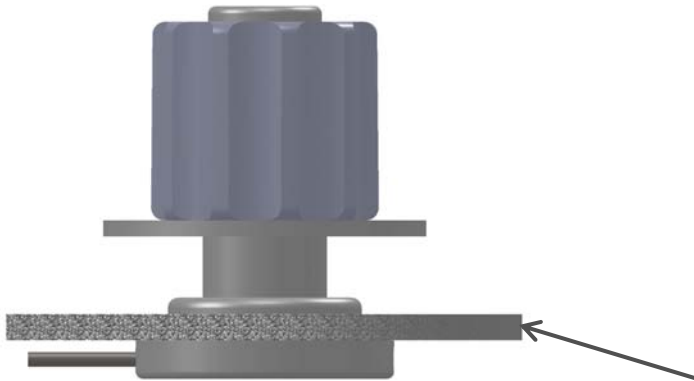
Non-clinical drug abuse liability testing

IV self-administration

How did we move on:

-Problem solving:

- the gauze pad underneath was modified in shape, size and material easy to insert subcutaneously; no irritation



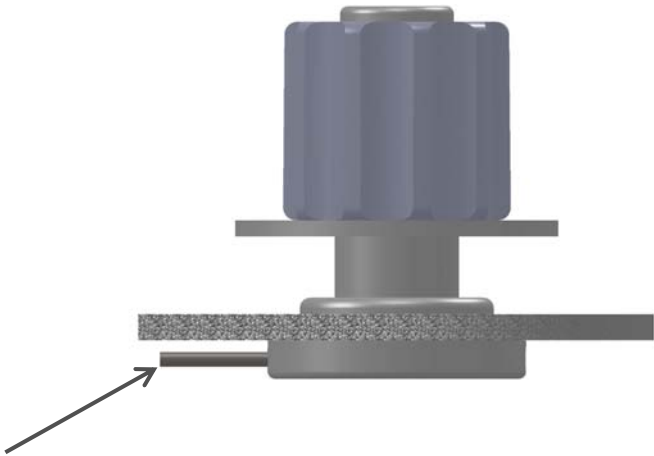
Non-clinical drug abuse liability testing

IV self-administration

How did we move on:

-Problem solving:

- the connection underneath between the VAB and the internal catheter was modified to avoid breaking loose

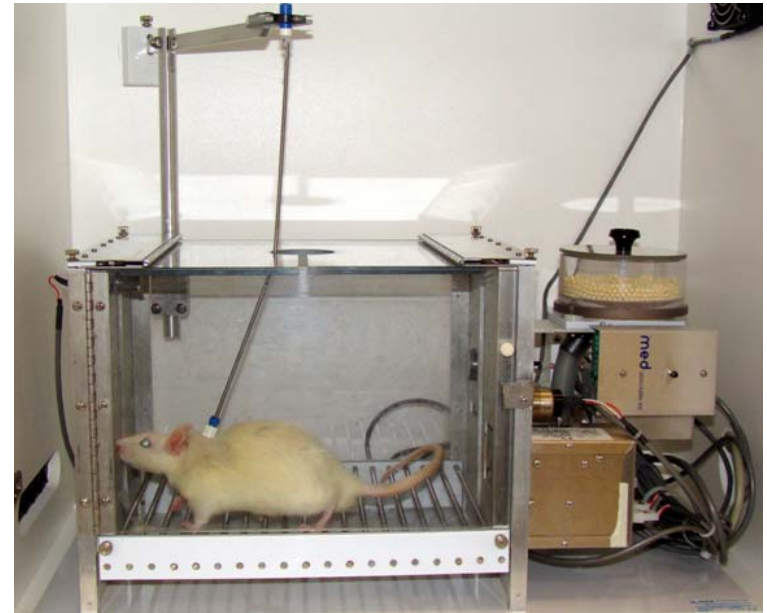
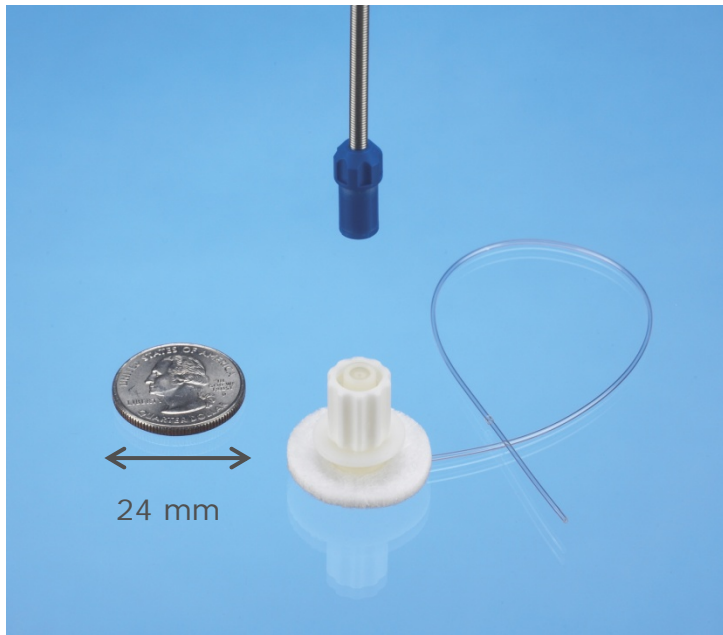


Non-clinical drug abuse liability testing

IV self-administration

Implementation of the VAB in the SA model

-Result: a new prototype of a modified vascular access button™ that can be used for long-term studies as in the SA model

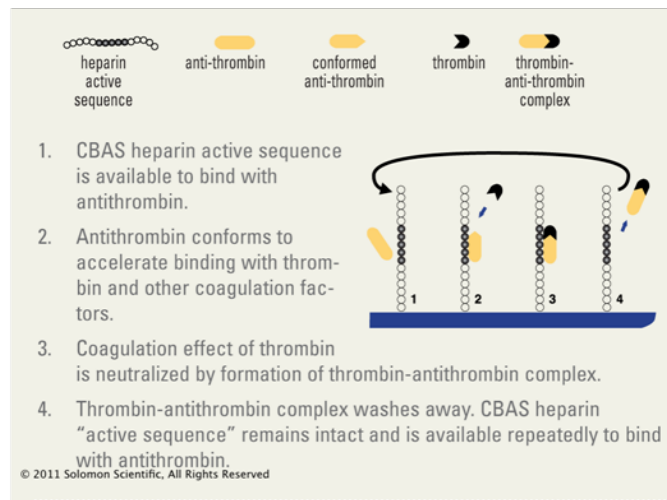


Non-clinical drug abuse liability testing

IV self-administration

Using the right catheter in the SA model

- catheter: brought into the v. Jugularis with the tip located near the right atrium
- choice of catheter: to be used for long-term studies as in the SA model
 - PU uncoated catheter: regular flushing needed (heparin solution)
 - PU coated catheter: CBAS® heparin coated PU catheter



The DSSc IV self-administration team



**INSTECH
SOLOMON**



Thank you