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## **The EMEA guideline on the non-clinical investigation of the dependence potential of medicinal products**

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## Background

- Medicinal products may cause dependence which is an unwanted side effect of these substances
  - Heroin: anti-tussant
  - Many opioids: analgesics
  - Cocaine: treatment of morfine addiction (S. Freud) and local anaesthetic in ophtalmology
  - Barbiturates: sedatives
  - Amphetamine:decongestant/appetite suppresssant/ADHD
  - Benzodiazepines: anxiolytics/sedatives
  - SSRI's: antidepressants

## Defining the issue (1)

- Dependence potential of a substance is the propensity of a substance, as a consequence of its pharmacological effects on physiological or psychological functions, to give rise to a need for repeated doses of the substance to “feel good” or to avoid “feeling bad.”
- More elaborate definitions of dependence syndrome for diagnosis in psychiatric practice in ICD-10 and DSM-IV
  - strong desire to take the drug
  - difficulties in controlling its use
  - persisting in its use despite harmful consequences
  - a higher priority given to drug use than other activities and obligations
  - increased tolerance
  - sometimes a physical withdrawal state

## Defining the issue (2)

- Psychological or psychic dependence
  - impaired control over drug use
  - craving, compulsion
  - involves reward mechanisms in brain
  - **Self-administration paradigm**
- Physical dependence
  - prevent appearance of withdrawal syndrome
  - may be preceded by tolerance
  - state of neuro-adaptation induced by repeated intake of a drug
  - **Observation of withdrawal symptoms**

## Defining the issue (3)

### Dependence potential

- Intrinsic pharmacological property
- Can be tested in a non-clinical model
- Positive signals need to be assessed in context of many other factors
  - pharmaceutical form
  - pharmacokinetics
  - clinical data
- Risk/benefit assessment
- Principal concern is medical use
- Secondary is control measures related to abuse

## Scope

- All new CNS-active substances
- Might not be needed for:
  - classes with well-documented absence of dependence potential extensive testing
  - classes with a well-described pharmacology related to dependence potential
  - radiopharmaceuticals and diagnostics given at low dose levels
- Compounds with new mechanism of action: testing is usually required
- Separate testing of metabolites may be needed
  - formed in humans
  - entering the brain in significant amounts
  - not adequately evaluated in animals administered parent

## Tiered approach

### First tier:

- early indicators
- signals from pharmacology and early toxicology studies

### Preliminary evaluation

### Second tier:

- Behavioural studies specifically designed to investigate dependence potential

# First tier: initial pharmacological characterisation

- *In vitro* studies
  - receptor binding
  - functional assays
  - targets of human origin, but where needed animal-derived receptors as well
  
- *In vivo* studies
  - CNS safety pharmacology
    - locomotor activity
    - stereotypical behaviour
    - sedation
    - antinociception
  - neuropharmacological models
    - microdialysis
    - neurotransmitter turnover

## Preliminary evaluation

- Consider all available evidence
- No further studies needed when:
  - No interaction at relevant concentration at known targets related to dependence potential, **or**
  - No functional effects at these targets; **and**
  - No signals from *in vivo* studies, **and**
  - Not a new mechanism of action
- Limited/no further studies required for compounds with obvious profile
- Compounds with new mechanism of action usually required
- Signals from subsequent (non)-clinical studies may prompt for reconsideration of initial decision

## Second tier: behavioural studies (1)

### General points

- Dose-effect curve should be investigated
- up to several times therapeutic concentration
- plasma kinetics of compound and metabolites
- route depends on model used
- responsive species, well-known models
- non-primate models preferred when feasible
- positive and negative controls
- multiple endpoints
- assess before, during and after treatment
- Choice of model depends on compound/class

## Second tier: behavioural studies (2)

### Studies investigating withdrawal (WS)

- adequate receptor occupation and development of neuroadaptive response
- usually clinical route
- careful definition of endpoints
- observation period long enough and frequency of observations sufficient
- both spontaneous and precipitated withdrawal possible
- tolerance is not a robust indicator for dependence
- various models can be used
- 'non-physical' or 'emotional' withdrawal phenomena like anxiety need special approach

## Second tier: behavioural studies (3)

### Studies investigating reinforcing properties

- self-administration (SA) paradigm
- intravenous route of administration
- design: flexible approach is acceptable
  - justification of choices is needed
  - effect on interpretation of results should be discussed.
  - progressive ratio relevant for relative potency
- drug history of animals
- other models may be used as well

## Second tier: behavioural studies (4)

### Drug-discrimination studies (DD)

- look for similarity to known classes in case of a novel class
- characterise when little experience is available with class
- DD alone does not comprise strong evidence of (absence of) dependence potential

## Specific classes of compounds (1)

- Classes with well-defined dependence potential and well-established models
  - opioids: both SA and WS. May have limited need for further studies
  - CNS-stimulants: SA
- Classes with less prominent dependence potential
  - sedatives and anxiolytics. Can cause withdrawal effects or have reinforcing properties, or both, or none. Both SA and WS would be needed.
- Classes with less experience in the medicinal field
  - NMDA antagonists
  - cannabinoids
  - nicotine-like compounds
  - Use of DD may be helpful. Use model most appropriate

## Specific classes of compounds (2)

- Monoamine reuptake inhibitors
  - SSRIs, SNRIs
  - Less well studied.
  - Non-clinical signals thus far rather weak
  - Clinical issue of discontinuation problems
  - Need for specific approach



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## Specific classes of compounds (3)

- Testing for non-physical withdrawal effects
  - Response in models for anxiety?
  - Sleep architecture?
  - CPA?
  
- Active substances with a new mechanism of action
  - Use of DD may be helpfull
  - Probe pharmacology and physiological sequelae
  - Use model most appropriate

## Timing of studies

- Receptor binding and CNS safety pharmacology before Phase 1
- Metabolite studies as soon as human PK data are available and relevant
- Serious concerns should prioritise behavioural dependence studies, generally before large studies (Phase 3)
- All information should be available before marketing authorisation application

## GLP

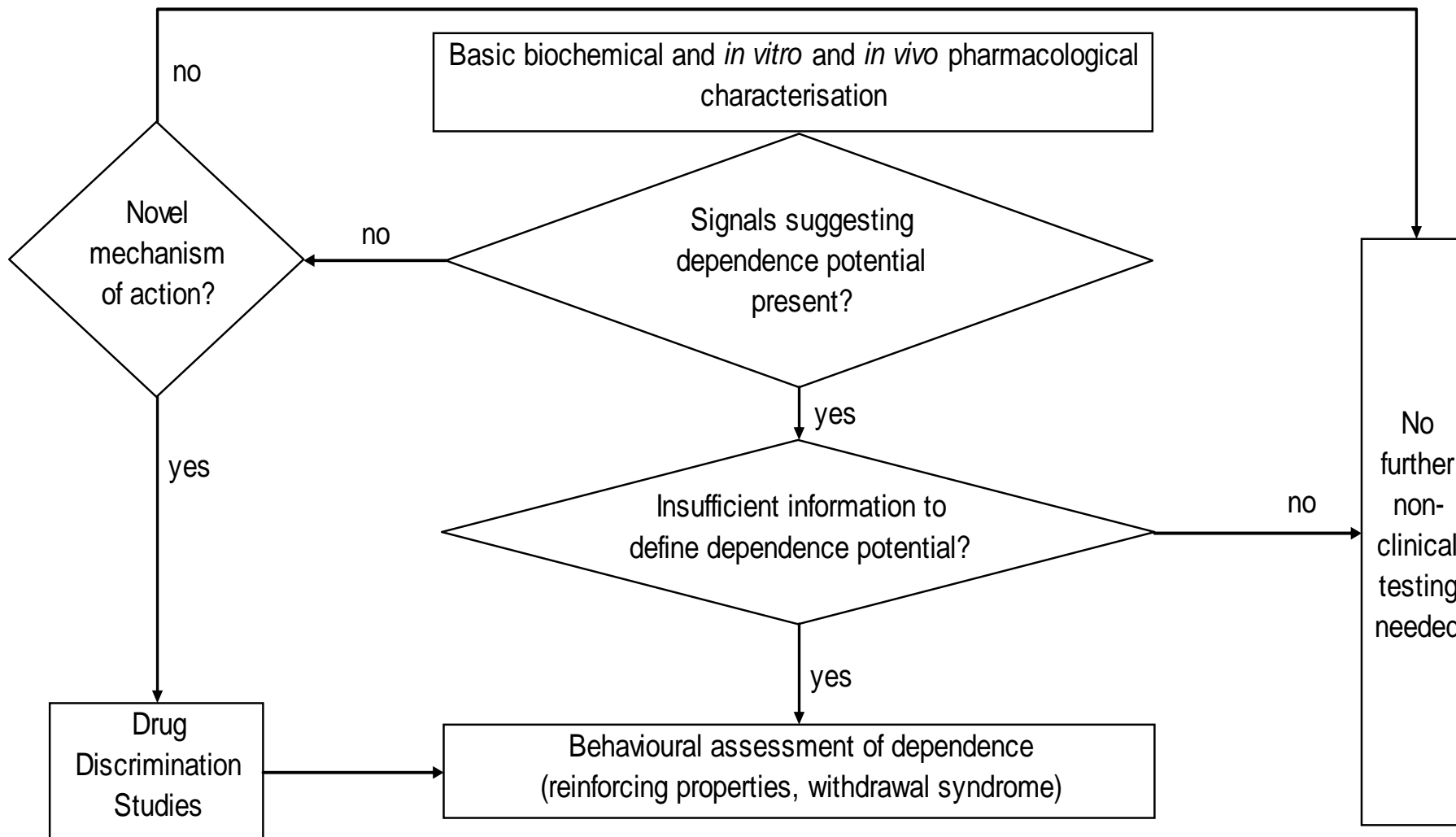
- receptor binding studies and basic *in vivo/in vitro* characterisation: = pharmacology – should meet high scientific standards
- Dependence potential is considered a safety issue: CNS safety pharmacology and behavioural studies (second tier) should conform to GLP
- Deviations from GLP should be justified and impact discussed.

## Integrative summary

- All non-clinical data should be integrated in a clear summary
- The clinical relevance of the non-clinical data should be discussed.

# Global decision tree

## Non-clinical testing of dependence potential of CNS-active compounds



**THE END**

**Thank you for your attention**