



European Medicines Agency  
*Evaluation of Medicines for Human Use*

London, 23 March 2006  
EMA/CHMP/SWP/94227/2004

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
(CHMP)**

**GUIDELINE ON THE NON-CLINICAL INVESTIGATION OF THE DEPENDENCE  
POTENTIAL OF MEDICINAL PRODUCTS**

<b>DRAFT AGREED BY SAFETY WORKING PARTY</b>	<b>February 2005</b>
<b>ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION</b>	<b>April 2005</b>
<b>END OF CONSULTATION (DEADLINE FOR COMMENTS)</b>	<b>31 October 2005</b>
<b>DISCUSSION IN THE SAFETY WORKING PARTY</b>	<b>December 2005 – February 2006</b>
<b>TRANSMISSION TO CHMP</b>	<b>March 2006</b>
<b>ADOPTION BY CHMP</b>	<b>March 2006</b>

## TABLE OF CONTENTS

EXECUTIVE SUMMARY .....	3
1 INTRODUCTION .....	3
2 SCOPE.....	4
3 LEGAL BASIS.....	4
4 TIERED APPROACH.....	4
<b>4.1 First tier: pharmacology .....</b>	<b>5</b>
4.1.1 <i>In vitro studies</i> .....	5
4.1.2 <i>In vivo studies</i> .....	5
4.1.3 <i>Evaluation</i> .....	5
<b>4.2 Second tier: specific behavioural pharmacology studies .....</b>	<b>6</b>
4.2.1 <i>General Points</i> .....	6
4.2.2 <i>Studies Investigating Withdrawal Syndrome and the use of data on tolerance</i> .....	6
4.2.3 <i>Studies Investigating Reinforcing Properties</i> .....	7
4.2.4 <i>Drug Discrimination Studies</i> .....	7
5 SPECIFIC CLASSES OF ACTIVE SUBSTANCES.....	8
<b>5.1 Opioids</b> .....	<b>8</b>
<b>5.2 CNS Stimulants</b> .....	<b>8</b>
<b>5.3 Sedatives and anxiolytics</b> .....	<b>8</b>
<b>5.4 Other classes</b> .....	<b>8</b>
<b>5.5 Novel classes</b> .....	<b>9</b>
6 TIMING OF THE STUDIES .....	9
7 GLP.....	9
8 DISCUSSION.....	9
REFERENCES .....	12

## EXECUTIVE SUMMARY

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.” Dependence potential is determined by those intrinsic pharmacological properties that can be measured in animal and human testing procedures for medicinal products. This guideline introduces a two-tiered approach to investigate the dependence potential of new CNS active substances. In the first tier, studies reveal the pharmacological profile of the active substance. Based on data from the first tier and other early indicators it should be decided whether subsequent behavioural studies investigating the reinforcing properties and potential to cause withdrawal phenomena is necessary. The guideline indicates which type of studies is needed and describes the minimum requirements of such studies, but a flexible approach is allowed, based on the type of active substance that is investigated. Reinforcing properties and physical withdrawal phenomena are well-known aspects of dependence potential. However, other aspects of withdrawal which are less clear by plain clinical observation, as exemplified by selective serotonin re-uptake inhibitors (SSRIs), also need to be evaluated. The relevance of the data for the assessment of human safety with respect to dependence potential of a medicinal product should be discussed.

## 1 INTRODUCTION

An active substance with dependence potential may cause a dependence syndrome, which has been defined in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, (ICD-10) as a cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a 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, and sometimes a physical withdrawal state [1].

Psychological or psychic dependence refers to the experience of impaired control over drug use (the related desire is often referred to as craving and the associated behaviour as compulsion). In a psychopharmacological context, physiological or physical dependence refers to a state of neuro-adaptation induced by repeated intake of a drug, necessitating continued drug administration to prevent the appearance of withdrawal syndrome on abrupt cessation of drug intake, which may be preceded by tolerance.

Dependence syndrome may develop in patients given the medicinal product for medical reasons, but may also occur in individuals taking it for non-medical reasons. When it is used for non-medical reasons often the term drug abuse is used. Drug abuse is defined as persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice. Moreover, dependence potential of the medicinal product may contribute to drug abuse but a medicinal product may have abuse potential, even in the absence of dependence potential. For further detail on the use of drug dependence terminology we refer to the reports of the WHO expert committee on drug dependence [2,3].

Whether a medicinal product may cause a dependence syndrome or lead to drug abuse is also influenced by other factors, for instance clinical (e.g. the occurrence of side-effects), social (acceptability of use), economic (availability and costs), chemical (ease of synthesis) and pharmaceutical. As these aspects are clearly not non-clinical, guidance on these aspects is not given in this guideline, but rather this guideline describes the need for testing of dependence potential in animals during the development of medicinal products and indicates what type of information is expected to support the assessment of human safety with respect to dependence potential of a medicinal product.

Besides well-known examples from the past like opiates, cocaine, amphetamine and barbiturates, more recent examples like benzodiazepines and SSRIs have been shown to be associated with withdrawal phenomena in some patients that may make it difficult to discontinue treatment. When discontinuation phenomena cannot be evaded by tapering down the dose – which is the standard approach – this syndrome may lead to drug dependence in these patients. Whereas benzodiazepines have been shown

to induce drug-seeking behaviour in animals and are associated with drug abuse in humans, this seems not to be the case for the SSRIs. Yet, retrospective review of all relevant non-clinical data on SSRIs by the CHMP [4] showed that for the majority of medicinal products the studies were not designed to study withdrawal phenomena and lacked sufficient observations in the critical period after stopping administration. Specific studies to investigate the reinforcing properties were only available for a few medicinal products. Furthermore, several symptoms associated with withdrawal reactions for SSRIs do not readily show by plain clinical observation of animals (*e.g.* paraesthesia, headache and anxiety). To detect such non-physical aspects of withdrawal new approaches are needed. Even though the SSRIs are not known to lead to drug abuse in humans, the withdrawal phenomena – currently often termed discontinuation syndrome – are relevant for the risk/benefit assessment of these medicinal products.

Clearly, there is a need for data from well-designed studies informing on the dependence potential of CNS active substances, including the occurrence of a discontinuation syndrome, whether or not this results in drug abuse [5]. The primary goal of these studies is to provide information on dependence potential relevant to the health care professional and the patient. The data should be suitable for the risk/benefit assessment of the medicinal product, the scientific underpinning of the Summary of Product Characteristics (SPC) and support regulatory decisions on the conditions of marketing authorisation. Non-clinical data obtained early during development may also be relevant for directing further clinical development of a medicinal product by providing early warnings of drug dependence-related problems.

## **2 SCOPE**

The need for dependence potential testing should be considered for all new CNS-active medicinal products. See also Note 1. If no studies are performed, the lack of these studies should be justified. New active substances, which act similar to active substances from a class with a documented absence of dependence potential, might not need testing for dependence potential. However for active substances with a new mechanism of action studies on dependence potential would usually be needed. Active substances from classes known to cause dependence would in general require limited testing to characterise the dependence potential and the extent of studying these properties needs to be determined on a case-by-case basis. Single dose radiopharmaceuticals or other diagnostic products given at similar low dose levels administered by professionals in a clinical setting are not within the scope of this guideline.

## **3 LEGAL BASIS**

The document should be read in conjunction with Directive 2001/83/EC (as amended) and all relevant non-clinical guidelines. The following guidance document is especially relevant: Position Paper on possible Pre-clinical Studies to investigate Addiction and Dependence/Withdrawal related to the use of SSRIs (CPMP/2278/00).

## **4 TIERED APPROACH**

Early indicators pointing towards dependence potential may be a chemical structure or a mechanism of action similar to any active substance known to have dependence potential, PK/PD characteristics (*e.g.* rapid onset/short acting active substances may be considered to have higher dependence potential), and pharmaceutical characteristics (information on route of administration, ease of administration, extraction, conversion, sublimation and solubility). Other early indicators arise from studies during early development investigating the pharmacological profile of an active substance. *e.g.* from receptor binding studies or pharmacology studies investigating CNS activity. In addition early indicators may come from pharmacokinetic studies (brain penetration, metabolites entering or formed in the brain) or repeated dose toxicology studies (abnormal behaviour or withdrawal symptoms in recovery periods). Further explorative studies may investigate the relevance of the early findings. Based on the level of concern, behavioural studies specifically designed to study dependence potential may be needed. Taking account of such a progressive non-clinical development of a medicinal product a two-tiered strategy is suggested.

Separate studies evaluating the dependence potential of metabolites would be needed when there is reasonable evidence that such metabolites are formed in humans, are suspected to penetrate the human CNS in significant concentrations and are not adequately evaluated in non-clinical studies with the parent.

## 4.1 First tier: pharmacology

### 4.1.1 *In vitro* studies

For CNS active substances receptor-binding studies are usually part of early development. The first signals pointing to dependence potential can be derived from these data, as binding of the active substance to known targets involved in drug dependence may be identified (e.g., opioid receptors, 5-HT and dopamine transporters and receptors, NMDA, GABA, nicotinic acetylcholine and cannabinoid receptors).

Functional assays at the cellular level to study whether binding to a receptor would also lead to functional cellular events are needed in clarifying the relevance and nature of such binding, e.g. whether the result is an agonistic or antagonistic effect. Examples of such assays are measurement of neurotransmitter release and second messenger activity. Whenever possible, targets of human origin should be used. But, where needed for the correct interpretation of animal studies, the affinity for and functional effects of the active substance at targets in non-clinical species should also be assessed.

### 4.1.2 *In vivo* studies

Further confirmation of the binding and functional properties observed *in vitro* can be obtained *in vivo*. Initial investigations could make use of neuropharmacological models, e.g. microdialysis (for example dopamine release in nucleus accumbens), neurotransmitter turnover, head twitch, antinociception and locomotor activity. Such studies – like the *in vitro* studies mentioned above – are considered supportive and help to elucidate the profile and mechanism of action of the active substance.

### 4.1.3 *Evaluation*

Once the biochemical and pharmacological profile of the active substance has been established to a sufficient degree, the need for a more elaborate assessment of dependence potential should be considered taking account of all relevant data, including other early indicators as mentioned at the start of this chapter.

Further studies investigating dependence might not be necessary when:

- no interaction at relevant concentrations with molecular targets considered relevant for dependence potential occurs, or when binding to relevant targets is observed, but this binding does not result in relevant functional effects; **and**
- *in vivo* investigations do not point towards dependence potential; **and**
- the active substance does not have a novel mechanism of action.

When the type and extent of dependence potential would already be obvious from the first tier (e.g. a full  $\mu$ -agonist), extensive testing in behavioural models may not be necessary.

If the active substance has a novel mechanism of action further studies should usually be undertaken.

If signals pointing towards drug dependence potential would emerge from subsequent studies in animals or man, an initial decision not to investigate dependence potential any further should be reconsidered.

At the end of this document a decision tree is included. The decision tree is not meant to provide a rigid scheme, but is meant to give a quick glance of the usual sequence of decisions, reflecting the guidance given in this guideline.

## 4.2 Second tier: specific behavioural pharmacology studies

### 4.2.1 General Points

Specific behavioural animal models have been developed for investigating dependence potential [6]. The choice of the model used should be justified based on the biochemical, pharmacological and clinical information already available. Pharmaceutical, pharmacokinetic and physico-chemical characteristics of the product may also influence the choice of the model. Specific aspects of dependence potential may require the use of different models.

Multiple endpoints would be needed, as no single measure of dependence potential is ideal.

Dependence potential should be studied over a wide dose range starting from threshold doses (showing no behavioural effects) up to doses corresponding to several-fold the expected human therapeutic exposure. The highest dose studied may include the maximum tolerated dose if this does not induce discomfort to the animal and cause unspecific behavioural changes potentially confounding the interpretation of the experiment [7]. Furthermore, an effect of an active substance on either motor function or learning and memory could affect the behavioural paradigms used to assess dependence potential and such considerations should be taken into account when designing the study. Plasma concentration measurements on the parent active substance and relevant metabolites should support the interpretation of the studies.

In principle, the clinical route of administration should be used, but different routes may be considered depending on the model used (see below), or taking account of the possibility of different routes in the context of non-medical use.

The animal species used should be responsive to the pharmacological effects of the active substance and sufficient documented experience with this species in dependence potential testing should be available. Where rodent or other non-primate models are available these deserve preference above primate models, provided the species chosen is appropriate for the active substance that is studied, the validity of the model used is sufficiently documented and the study is technically feasible in the chosen species. There is no need for routine confirmatory studies in primates, but a primate study may be appropriate when there is uncertainty concerning the results and interpretation of the non-primate studies, or other data (e.g. clinical) are conflicting with the results from non-primate studies.

Negative controls (vehicle) should be used. Positive controls should be included to demonstrate the validity of the experiment, unless sufficient documented data is made available to show the validity of the assay used. Where possible, the positive control should be a prototype active substance of the class to which the investigational active substance belongs. However, if this is not possible, i.e. for NCE's with a novel mode of action or with atypical actions, then the positive control chosen should be selected based on the similarity of the behavioural pharmacology of the NCE and the positive control chosen (e.g. CNS depressant or CNS stimulant). Here, the results from drug discrimination studies may provide relevant clues.

In behavioural models multiple endpoints should be examined, e.g. motor function, cognitive function and appetitively motivated behaviour. The different endpoints should be monitored before, during and after treatment. This would facilitate further characterisation of the extent and nature of undesirable behavioural consequences of the active substance, give reassurance that a behaviourally effective dose is studied and might give information of tolerance phenomena.

### 4.2.2 Studies Investigating Withdrawal Syndrome and the use of data on tolerance

The activity of CNS active substances is based on their interaction with neuronal targets. This interaction may lead to neuroadaptive responses, which may be essential for the effectiveness of the medicinal products. When the active substances are withdrawn, the altered state of the CNS may be revealed by the emergence of a withdrawal syndrome (now often named discontinuation syndrome), which is specific for the active substance. Non-clinical studies may provide more systematic insight in withdrawal phenomena. Specific considerations to be taken into account for these types of study are:

- The dose, frequency and duration of treatment needs to be sufficient to ensure relevant exposure, to cause adequate receptor occupancy and/or brain penetration and to allow the animal to develop a neuroadaptive response;
- Careful definition of the endpoints (behaviour, body temperature, body weight, food intake); and if behaviour is taken as an endpoint, various possibilities can be used – i.e., gross behaviour, locomotor activity, instrumental behaviour or sleep wakefulness cycle;
- Observations should be made for a period long enough and with a frequency sufficient to detect all signs of withdrawal. Also the duration of measurement of baseline behaviour should be sufficient to make a comparison of post-treatment behaviour with baseline meaningful.

Both studies on spontaneous withdrawal and precipitated withdrawal (using an antagonist) may be used.

To investigate the ‘emotional element’ of withdrawal, specific models may be used, *e.g.* sensitivity to anxiogenic stimuli in various models and conditioned place avoidance models.

Tolerance is a decrease in response to a active substance dose that occurs with continued use and which may be revealed in various studies as a time-dependent change in the dose-response relationship. Functional tolerance is defined as a decrease in sensitivity of the central nervous system to the active substance. As such the observation of functional tolerance reveals an aspect of neuroadaptation and may contribute to the development of dependence. However, tolerance is not regarded a robust marker and may occur without the development of dependence. Next to functional tolerance, metabolic tolerance may occur, which is the result of increased clearance of the active substance. Metabolic tolerance is a separate phenomenon and does not contribute to drug dependence. Studies on cross-dependence and cross-tolerance may be supportive for further characterisation and comparison with other active substances (NOTE 2).

#### 4.2.3 *Studies Investigating Reinforcing Properties*

Concerning the reinforcing properties of active substances, the self-administration paradigm is most widely used and may be seen as an approach with great face validity. Points to consider for these types of study are:

- The route of exposure. If technically feasible, the intravenous route of administration should be used, as this would facilitate an almost immediate availability of the active substance to the brain. In that way the association between the drug-taking behaviour and the drug-effect is more readily made;
- Design of the study, *e.g.* the use of timeouts (non-availability of the active substance) in relation to the occurrence of toxic side effects, the schedules of reinforcement used and the use of substitution procedures. All of these aspects affect the suitability of the model and the interpretation of the results. A flexible approach is acceptable, but the design of the study should be justified and the potential effects it may have on the interpretation of the results should be discussed... When possible, progressive ratio-schedules should be used to allow assessment of relative reinforcing efficacy (i.e., “break-point”);
- Previous use of animals. The drug history of the animals may affect the outcome of the study. This may especially be the case when measurements are made shortly after substitution.

Other models may be used as well, for instance conditioned place preference to study rewarding properties of active substances. Especially where new classes of active substances are tested the need for a flexible approach is acknowledged.

#### 4.2.4 *Drug Discrimination Studies*

When an active substance from a novel class is investigated drug-discrimination studies may be used to assess the similarity of the interoceptive cue of the active substance with those of prototypic active substances of known classes of active substances causing dependence. However, generalisation with

an active substance known to cause dependence in itself is not necessarily indicative of dependence potential...

## **5 SPECIFIC CLASSES OF ACTIVE SUBSTANCES**

### **5.1 Opioids**

For opioids both physical and psychological dependence are relevant. Different models may be used to assess these aspects. Often data from basic pharmacology studies, e.g. receptor binding and activity profile and acute pharmacological effects can be predictive of the dependence potential of active substances in this class. Isolated organ preparations or recombinant receptor systems may be used to study the affinity for different receptor subtypes. Sometimes, e.g. in case of full  $\mu$ -agonists this may be sufficient and no further studies would be needed. However, new molecular entities from this class more often show mixed profiles and further studies to characterise the dependence potential would be necessary.

### **5.2 CNS Stimulants**

Whether an active substance is a CNS stimulant actually can only be concluded after behavioural studies in animals have been performed or relevant observations in humans have been made. However, dopaminergic properties, particularly in mesolimbic and mesocortical regions, might be considered a signal suggesting the active substance has reinforcing properties. Such properties can be investigated in a self-administration paradigm. A positive response in a self-administration study is a strong signal indicating dependence potential of an active substance. Yet, in humans such an active substance may not necessarily cause dependence. Other pharmacological properties (e.g. emetogenic) may limit the use in humans. Some therapeutic classes (for example appetite suppressants and medicinal products indicated for Attention Deficit Hyperactivity Disorder (ADHD)) may be associated with reinforcing properties. Medicinal products belonging to such classes should be investigated using the drug self-administration model.

### **5.3 Sedatives and anxiolytics**

This is a diverse group of active substances including benzodiazepines, barbiturates and other sedatives/hypnotics. A common pharmacological property is the sedative activity. Physical dependence presenting as a withdrawal syndrome is a prominent aspect of dependence potential of these active substances. But benzodiazepines have also been shown to induce self-administration in animals after intravenous administration, suggesting reinforcing properties as well. Thus, the sedative activity itself is not predictive of the type of dependence potential. Therefore sedatives and anxiolytics of which the type of dependence potential is not self-evident (from the pharmacological properties assessed in the first tier and from the similarity to known active substances) should be investigated both for their potential to induce self-administration and for the occurrence of withdrawal phenomena.

### **5.4 Other classes**

Active substances belonging to classes containing examples of active substances with dependence potential, e.g. NMDA-antagonists, cannabinoids and nicotine-like active substances should be investigated for drug dependence potential. Drug discrimination studies may reveal the similarity of the new active substance with a standard from the same class. Dependence potential should be further investigated using the models most appropriate for the class.

Concerning SSRIs, thus far evidence from well-designed pre-clinical studies with respect to dependency and withdrawal is incomplete [5]. Members from this class as well as other monoamine reuptake inhibitors should be scrutinised more thoroughly for dependence potential. This would involve both measures of physical dependence investigating the potential to cause withdrawal symptoms as well as studies investigating the reinforcing properties of the active substance. [NOTE 3].

## 5.5 Novel classes

Of major concern, but at the same time most challenging is the study of the dependence potential of active substances belonging to novel pharmacological classes where no class-specific standards may be available for reference, and the dependence potential has yet to be established. The pharmacological profile at the level of receptor binding and activity may serve as a starting point. Observations made in pharmacological studies *in vivo* may also provide relevant information. If these data provide insufficient clues, active substances with a new mechanism of action could be investigated for similarity of the interoceptive cue of the active substance with those of prototypic comparators of known classes of active substances causing dependence. Based on the information available suitable models have to be chosen to elucidate the dependence potential further. Well-designed studies investigating the potential to induce withdrawal phenomena, as well as investigation of reinforcing properties of the active substance are considered a minimum.

## 6 TIMING OF THE STUDIES

Receptor binding studies and safety pharmacology studies regarding the CNS as outlined under ICH S7A should be completed before phase 1 clinical trials. This would facilitate anticipation towards the dependence potential of the active substance and provide information for direct clinical monitoring. Further investigation of dependence potential can be undertaken alongside clinical development. Safety signals in this respect seen during early non-clinical or clinical studies could be a reason to prioritise further non-clinical dependence studies. In case of a serious concern and insufficient data for a proper risk assessment more detailed information might be needed before large groups of patients are exposed for an extended period of time during clinical development. In general, metabolites do not need to be evaluated for dependence potential prior to human trials. Separate receptor binding studies on metabolites should be initiated as soon as human pharmacokinetic data are available and such studies are considered appropriate. When studies on metabolite receptor affinity and other studies described under the first tier are deemed relevant, data from these studies should become available before large populations are exposed to the investigational medicinal product, generally before Phase III. All relevant data should be available at the time of a Marketing Authorisation Application.

## 7 GLP

Studies referred to under the first tier – except those belonging to the safety pharmacology regarding the CNS as outlined under ICH S7A - generally do not need to meet the requirements of GLP, although scientifically high standards should also be maintained in these studies. Safety pharmacology studies should comply to GLP, as outlined in ICH S7A. The behavioural pharmacology studies for investigating dependence potential referred to in the chapter on the second tier should be conducted in compliance to GLP to the greatest extent possible. When studies are not conducted in compliance with GLP, study reconstruction should be ensured through adequate documentation of study conduct and archiving of data. Any study or study component not conducted in compliance with GLP should be adequately justified, and the potential impact on evaluation of the behavioural pharmacology endpoints should be explained.

## 8 DISCUSSION

All relevant non-clinical data should be integrated in a clear summary. The clinical relevance of these data for medical use, as well as their relevance for potential non-medical use should be discussed. This discussion should address the possibility that the active substance can lead to dependence syndrome or induce a discontinuation syndrome.

### NOTE 1

In general, only CNS active substances are of concern. However, active substances with peripheral targets may enter the brain as well either as parent active substance or as a metabolite at relevant concentrations and interact at central targets. This could be a concentration dependent phenomenon, the result of applying different routes of administration or a consequence of metabolism. When available data give rise to a concern in this respect studies as explained in this document should be considered to further clarify the pharmacological profile of the product.

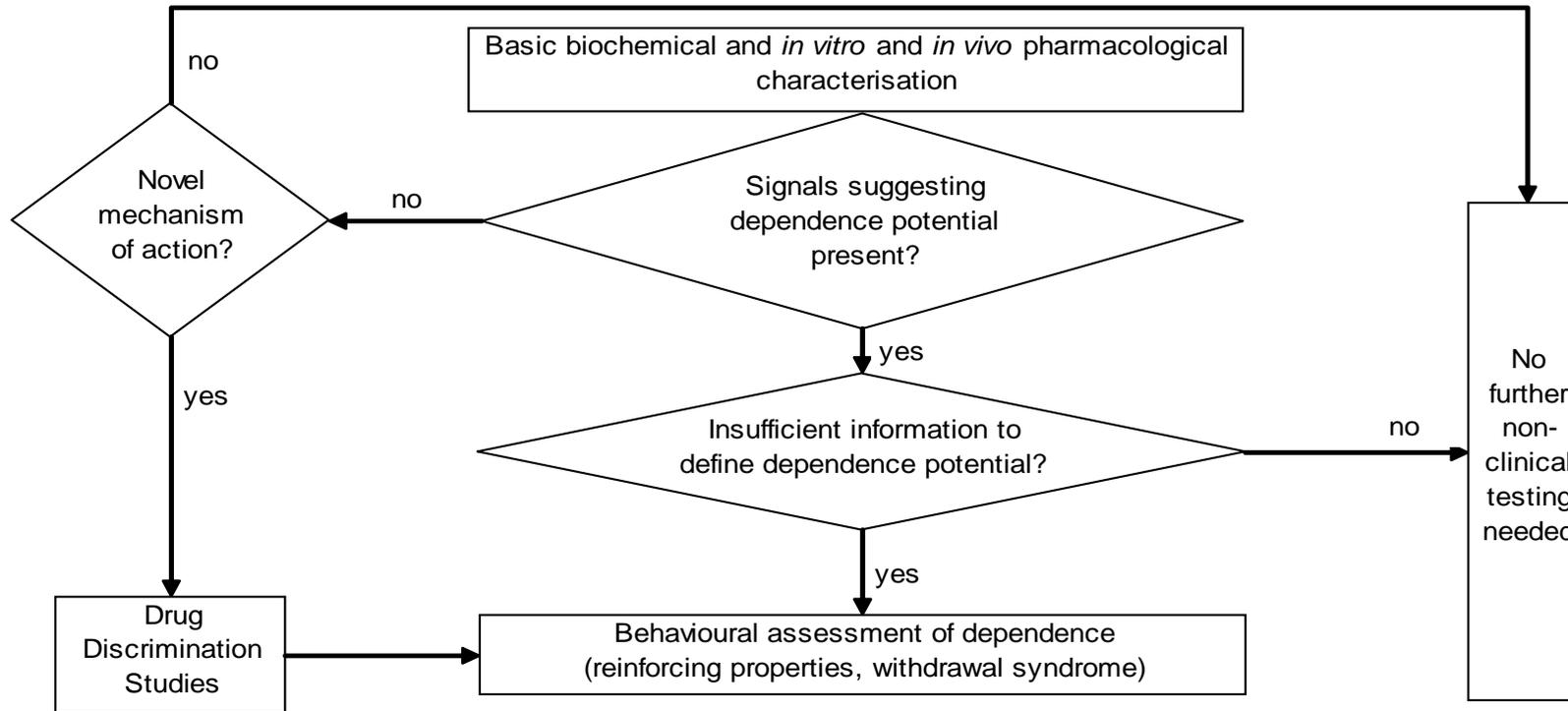
## **NOTE 2**

Cross-dependence studies investigate whether an investigational active substance can substitute for an active substance with a known withdrawal syndrome - or vice versa – by preventing the emergence or amelioration of the withdrawal syndrome. Cross-tolerance is defined as the development of tolerance to an active substance following the administration of another active substance. Cross-dependence studies and cross-tolerance studies can be informative, but have their limitations and difficulties with interpretation and appear to have limited value for active substances with novel mechanisms of action.

## **NOTE 3**

Currently, it is difficult to define specific guidance on which model to use and which parameters to assess when studying dependence potential of SSRIs and related active substances. Some suggestions are given in the CPMP position paper [5]; however, this remains an area that still needs further development.

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



## REFERENCES

1. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, 2<sup>nd</sup> edition (ICD-10). World Health Organisation. ISBN 92 4 154660 3.
2. WHO Expert Committee on Drug Dependence. Twenty-eight report. Geneva. World Health Organisation, 1993 (WHO Technical Report Series, No. 836).
3. WHO Expert Committee on Drug Dependence. Thirty-third report. Geneva. World Health Organisation, 2002 (WHO Technical Report Series, No. 915).
4. CPMP position paper on selective serotonin uptake inhibitors (SSRIs) and dependency/withdrawal reactions. EMEA/CPMP/2775/99, 12 April 2000.
5. CPMP position paper on possible pre-clinical studies to investigate addiction and dependence/withdrawal related to the use of SSRIs. CPMP/2278/00, 14 December 2000.
6. Balster RL and Bigelow GE. Guidelines and methodological reviews concerning drug abuse liability assessment. *Drug and Alcohol Dependence* 70 (3, Suppl. 1):S13-S40; 2003.
7. Ator NA. and Griffiths RR. Principles of drug abuse liability assessment in laboratory animals. *Drug and Alcohol Dependence* 70 (3, Suppl. 1):S55-S72; 2003.