European Medicines Agency
Evaluation of Medicines for Human Use

London, 17 November 2005
Doc. Ref. EMEA/CHMP/EWP/369963/2005

COMMITTEE FOR MEDICAL PRODUCT FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON THE DEVELOPMENT OF NEW PRODUCTS FOR THE TREATMENT OF TOBACCO AND ALCOHOL DEPENDENCE

AGREED BY THE EFFICACY WORKING PARTY	September 2005
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	17 November 2005
END OF CONSULTATION (DEADLINE FOR COMMENTS)	28 February 2006

Comments should be provided to Line.Jensen@emea.eu.int
Fax: +44 20 7418 86 13

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 60
E-mail: mail@emea.eu.int http://www.emea.eu.int

1. INTRODUCTION

According to the definition of World Health Organisation[1], ICD-10, and DSM-IV-TR, dependence on substances is characterised by a cluster of physiological, behavioural and cognitive phenomena, in which the use of a substance takes on a much higher priority for an individual than other behaviours that once had greater value. Criteria for diagnosis of dependence are, among others, a strong desire or compulsion to take the substance despite knowledge or evidence of its harmful consequences, difficulty in controlling the level of its use, physiological withdrawal symptoms and development of tolerance. People could become dependent on the use of a wide range of substances like tobacco, caffeine, alcohol, opioids, sedatives and hypnotics, cocaine and other psychoactive stimulants, volatile solvents, cannabinoids and hallucinogens. The use of these various substances may lead to harmful physical and psychological consequences, e.g. cancer and COPD in tobacco smokers, liver cirrhosis in heavy alcohol consumption and alcohol abuse and depression following the use of MDMA (ecstasy)[2]. The rate of social acceptance may also influence the consequences of dependency, e.g. the use of sedatives and tobacco is generally more accepted than the use of heroin. The prevalence of substance dependences is high. The prevalence of alcohol dependence in several European countries was estimated as 5.2%[3] and of smoking between 22-47%[4]. Medicines that are currently used for the treatment of dependence are either substitutes (e.g. nicotine, methadone), antagonists (e.g. naltrexone) or atypical antidepressants (bupropion[5] for smoking cessation). Disulfiram interferes with alcohol metabolism, causing accumulation of toxic acetaldehyde and consecutively severe headache and nausea and can be classified as aversive treatment modality. Acamprosate, a GABA agonist and glutamate antagonist, is used in several EU countries for preventing relapses in abstinent alcohol users.

2. PROBLEM STATEMENT

Dependency could occur to a very wide range of substances, which may need specific treatment approaches. It is therefore hard to develop a general Note for Guidance for all kind of addictions. We propose to focus in first instance on substances where new treatment alternatives are in the pipeline or expected to be developed in due time, namely tobacco smoking and alcoholism.

There is no *opinio communis* in Europe about the optimal treatment for opioid, cocaine and amphetamine addiction. In some European countries treatment is mainly focussed on absolute abstinence, while in other countries low-threshold treatment centres with emphasis on harm-reduction may also be acceptable. It is not expected that a European consensus document for these addictions is feasible. Therefore, we propose to postpone to include these substance abuses in this guidance document, and to focus in first instance on treatment of tobacco and alcohol use. However, when new developments will arise, these topics could become subject of additional guidances.

The guidance is neither intended for treatment options of acute overdose symptoms. Recently, a draft EMEA guideline became available on the non-clinical investigation of the dependence potential of medicinal products.[8]

3. DISCUSSION (ON THE PROBLEM STATEMENT)

For clinical trials on new products, a clear definition of tobacco/alcohol dependence should be defined. For instance it should become clear whether binge drinking or social drinking would be included. Main target group will be however, the subjects with addiction and/or dependence. Subsequently, clinical endpoints should be defined, e.g. whether this should comprise complete cessation or less strict criteria. In addition, the clinical relevance of the chosen endpoint should be substantiated. The inclusion or exclusion of certain populations, e.g. certain age groups or dual diagnosis patients, should be motivated.

Duration of studies (short- and long term studies) and the appropriateness of using a 3-arm design including placebo and a comparator should be discussed. In addition, the use of concomitant treatment, e.g. role of therapeutic counselling, switching to other forms of abuse and its consequences for efficacy outcome should be evaluated. Appropriate safety monitoring will be mandatory according to standard procedures.

Further whether harm reduction may be accepted as an indication and the implications for study design may be discussed.

4. RECOMMENDATION

Regulatory guidance on the development of medicinal products for the treatment of alcohol and tobacco dependence is currently not available, whereas several products have been recently developed or are under development. It is recommended to draft two guidance documents, one for tobacco dependence and one for alcohol dependence. In these guidance documents, specific attention should be drawn to clear definitions of the targeted treatment population, appropriate endpoints, study design and need for comparative studies.

5. PROPOSED TIMETABLE

It is anticipated that draft CHMP guidance documents may be available 12 months after adoption of the Concept Paper.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this Guideline will only involve the EWP.

7. IMPACT ASSESSMENT (ANTICIPATED)

It is aimed that the "Note for Guidance on the development of new products for the treatment of dependence on tobacco and alcohol" will be helpful to achieve more consensus in evaluation of such products by regulatory authorities. Furthermore, it is expected that such guidance document would improve quality and comparability of submitted studies by pharmaceutical industries.

8. INTERESTED PARTIES

- European College of Neuropsychopharmacology

9. REFERENCES TO LITERATURE, GUIDELINES ETC

1 http:/www.who.int/substance_abuse/terminology/definition/en/print.html

2 de Win MM, Reneman L, Reitsma JB, den Heeten GJ, Booij J, van den Brink W. Mood disorders and serotonin transporter density in ecstasy users--the influence of long-term abstention, dose, and gender. Psychopharmacology 2004;173:376-82.

3 Alonso J., et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project.Acta Psychiatr Scand Suppl. 2004;420:21-7.

4 http://www.data.euro.who.int/Default.aspx/TabID=2444

5 Holm KJ and Spencer CM. Bupropion. A review of its use in the management of smoking cessation. Drugs 2000; 59: 1007-1024

6 Boothby LA, Doering PL. Acamprosate for the treatment of alcohol dependence. Clin Ther. 2005;27:695-714.

7 Note for Guidance on Clinical Investigation of Drugs Used in Weight Control, CPMP/EWP/281/96

8 Guideline on the Non-Clinical Investigation of the Dependence Potential of Medicinal Products, Draft, London, 21 April 2005, EMEA/CHMP/SWP/94227/2004