European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 24 January 2008
Doc. Ref. EMEA/CHMP/EWP/20119/2008

COMMITTEE FOR MEDICAL PRODUCT FOR HUMAN USE (CHMP)

DRAFT

CONCEPT PAPER ON DEVELOPMENT OF GUIDELINE ON THE TREATMENT OF ATTENTIONAL DEFICIT HYPERACTIVITY DISORDER (ADHD)

AGREED BY EFFICACY WORKING PARTY	January 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 January 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 April 2008

Comments should be provided to EWPsecretariat@emea.europa.eu
Fax +44 20 7418 8613

KEYWORDS	*CHMP, EMEA, Concept Paper, Drug Evaluation, Drug Approval, ADHD, children, adults, psychostimulants*

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eu.int http://www.emea.eu.int

1. INTRODUCTION

Child psychiatric disorders have so far only been modestly in the scope of regulatory authorities, because their treatment was not primarily based on pharmacotherapy. Yet, the field is changing and moving fast towards new insights in aetiology and treatment strategies[1]. With the new legislation coming into effect in 2007, the development of products for use in children will be stimulated[2]. It is therefore time to anticipate on forthcoming studies in the child psychiatric field and provide guidance for industry and regulatory bodies to enable licensing of products on the best attainable efficacy and safety data.

So far, recommendations for clinical trials in adolescents and children are incorporated in different guidelines for *adult* psychiatric disorders, i.e. depression, anxiety, bipolar disorder and schizophrenia, on the basis of the possibility to extrapolate.

Attention Deficit Hyperactivity Disorder, ADHD, is a well defined disorder with core features such as hyperactivity, inattentiveness and impulsivity, that has its origin in childhood and for which pharmacotherapy is more or less among the standard care. It has long been acknowledged that the core symptoms of ADHD ameliorate with age. It has only recently been recognized that symptoms may persist into adulthood, thereby extending pharmacotherapy to this age group. With the development of new products and new formulations of existing products, the present guideline may serve as guidance to address specific problems in the clinical trial design that are encountered in the treatment of childhood onset psychiatric disorders (age cohorts, co-morbidity, brain development and maturation).

2. PROBLEM STATEMENT

ADHD is one of the most prevalent disorders of childhood, its worldwide prevalence being estimated at approximately 5-6%[3]. It is estimated that boys are more affected than girls. Psychostimulants such as methylphenidate and more recent atomoxetine are, pharmacologically, the treatments of choice. New products are in the pipeline that are aimed at being devoid of stimulant effects, and provide a more favourable safety profile.

Adult ADHD is now recognised as symptoms persisting into adulthood. Often, the disorder is limited to ADD, hyperactivity not being one of the core features, but inattentiveness and difficulty concentrating/planning. With AD(H)D covering all age ranges, specific problems are inherent, i.e. different co-morbidity, proper diagnosing, different efficacy and safety, and even benefit/risk.

So far, products have been licensed for children, based on (in general) relatively short trials, little non-clinical juvenile data and almost no prospective safety especially long-term data. With the current knowledge of brain development and maturity, availability of more sophisticated instruments to measure cognition, and availability of a juvenile toxicity guideline, all these aspects require attention in the clinical trial design and post-marketing surveillance of new products.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

In the present guideline, guidance should be given to:

- The target population
- Duration of trials, short-term efficacy and maintenance of effect
- Long-term safety, including effects on growth, development and sexual maturity, cognition
- The use of a comparative design
- The different age cohorts to be treated (pre- and post pubertal, adulthood)
- The presence and acceptance of co-morbidity
- The validity of age related diagnostic instruments, measurement tools, and observer or subject ratings
- Definition of age related endpoints

4. RECOMMENDATION

Regulatory guidance on the development of medicinal products for the treatment of child psychiatric disorders per se is currently not available. ADHD is a common and well diagnosed entity for which several products are developed and new treatment options are aimed for. In this guidance document, specific attention should be drawn to clear definitions of the targeted treatment population, specific age-category problems (childhood versus adolescence and adulthood), appropriate endpoints, study design, need for comparative studies, and long-term safety.

5. PROPOSED TIMETABLE

It is anticipated that draft CHMP guidance documents may be available 6 months after adoption of the Concept Paper.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this Guideline will 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 ADHD" will be helpful to achieve more consensus in the 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

The Dutch Society of Psychiatry, department of Child and Adolescent Psychiatry

National Center of Expertise Child- and Adolescentpsychiatry (Landelijk kenniscentrum Kinder- en Jeugdpsychiatrie)

Center of Expertise ADHD in Adults (Kenniscentrum ADHD bij volwassenen)[x]

Medical Network ADHD (Artsen Netwerk ADHD)

9. REFERENCES TO LITERATURE, GUIDELINES ETC

1 Verheij F, Verhulst FC, Ferdinand RF. Tijdschr Psychiatr. 2007;49(7):429-38.

2 http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics

3 Polanczyk G, Silva de Lima M et al. 2007. The worldwide prevalence of ADHD: A Systematic Review and Metaregression Analysis. Am J Psychiatry 164:942-948

GUIDELINE ON THE NEED FOR NON-CLINICAL TESTING IN JUVENILE ANIMALS ON HUMAN PHARMACEUTICALS FOR PAEDIATRIC USE (CHMP/SWP/169215/2005)

NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION (CPMP/ICH/2711/99)