04 August 2010
EMA/CHMP/EWP/12575/2010
Committee for Medicinal Products for Human use (CHMP)

Overview of comments received on 'Guideline on the clinical investigation of medicinal products for the treatment of attention deficit hyperactivity disorder (ADHD)' (EMEA/CHMP/EWP/431734/2008)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	European College of Neuropsychopharmacology (ECNP) I
2	European College of Neuropsychopharmacology (ECNP) II
3	Shire Pharmaceuticals
4	European Association for Clinical Pharmacology and Therapeutics (EACPT)
5	EFPIA
6	EUNETHYDIS Guidelines Group
7	International Federation of Associations of Pharmaceutical Physicians (IFAP)
8	J&J
9	H. LUNDBECK A/S
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1. GENERAL COMMENTS – OVERVIEW:

Stakeholder No.	General Comment (if any)	Outcome (if applicable)
1	Only very limited comments were provided on this document (see below). However, as they clearly indicate a lack of clarity, we feel they may still help the EMEA to improve the document. 1. This an important but too generic guideline that fails to provide specific detailed information and would benefit from some revision; 2. There need to be clear criteria by which an investigational compound could be designated as an 'orphan drug'; 3. Whilst providing these, there should also be limits set by which the term 'orphan drug' is used; 4. However general, the document is potentially useful, if developed in this way.	1. An attempt is made to be more specific at several places in response to the overall comments. 2. n.a. 3. See answer to 2. 4. See previous answers.
2	In general the guideline is written clearly and addresses the main issues and problems related to clinical investigation in ADHD. Due to safety concerns, and given that ADHD treatment can also be studied in adults, novel compounds should be tested first in adults. Therefore, it should be stated that novel compounds first be investigated comprehensively in adult ADHD patients for efficacy and long-term safety, prior to any subsequent clinical studies in children and adolescents.	ADHD is a disorder with childhood onset origin. Symptoms may change over time, i.e. from childhood to adolescence, to adulthood, thereby challenging diagnostic certainty over time and related outcome of efficacy/safety. Persistence of the innate disorder is recognized. Therefore, PK and tolerance may be first tested in adults, but clinical studies should be started in children, although they may run in parallel with adults. Text amended under 6.1.2.
3	The Company welcomes the availability of this guideline providing detailed advice on developing ADHD medications for European patients and appreciates the opportunity to provide comments. In general, the Company would like to strongly suggest that there are aspects of the development strategy that are dependent on the characteristics of the drug class under investigation. Specifically, study interval lengths should be chosen based on the well-characterised differences in the neuropsychopharmacological mechanism of action for stimulant medications as compared to non-stimulant medications. Further detailed information and comments are presented in Section 2 below.	With the recommendation of short-term studies of 6 weeks duration on stable dose, the differences between stimulant and non-stimulant drugs are considered sufficiently covered. In addition, by using this criterion as compromise between the different drugs that may be tested in the future, the data outcome allows for comparison between trials, and will facilitate the regular update of the guideline at due times. No text amendment necessary at this moment.
4	Overall agreement, but see specific comments.	

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5	The Agency has done an outstanding job of providing guidance to industry on the clinical investigation of pharmacologic products for the treatment of ADHD and acknowledging it's substantial impact, not only in child- and adolescent psychiatry, but that signs and symptoms also persist into adulthood and the need for new treatments.	
	The proposed guidance represents a positive step to addressing challenges in drug development for ADHD and provides industry with insight to the Agency's current thinking. While we agree that the guideline is useful, we believe that equal emphasis should be given in the guideline to the treatment of ADHD in all target age groups, including adults. The guideline relegates adults to the special population section; potentially giving the impression that ADHD development programs should address treatment of ADHD in children first. Adult ADHD is a valid target for initial study of ADHD. In fact, in some cases, adult patients may be the preferred population to study novel compounds where it is desirable to reduce exposure in vulnerable paediatric patients and to minimize their exposure to the extent possible until efficacy / safety in adults have been established.	The comment has been well taken. Yet, for reasons of assay sensitivity and diagnostic validity of the ADHD syndrome, studies in children prior to, or at least in parallel with, studies in adult.s is the preferred strategy. PK/tolerance studies may be started in adults for safety reasons. See text adjustment under 6.1.2
	The importance of having symptoms prior to age 7 (for adults and children) is emphasised. This age cutoff is not well supported by data and there are conflicting data showing that outcomes are the same for patients diagnosed as adults (without clear history of childhood symptoms) and adult patients with recorded childhood symptoms. This prevents someone from ever being diagnosed with ADHD if they didn't have an observant reporter available during childhood since the guidance itself points out that the patient is not a reliable reporter at young age.	For a diagnosis of ADHD in adulthood, the verifiable presence of symptoms in (early) childhood is mandatory. The word 'early' is put between brackets. Further text amendments are made to illustrate what is meant by verifiable symptoms 'e.g. medical records, school reports'.
	The diagnosis of ADHD described in this guideline is based on DSM-IV, which is currently under review and being updated. Therefore, a general comment should be included in the guideline that "While diagnosis and study design recommendations apply to drugs under development at the time the guideline was developed, consideration must always be given to the evolution of clinical practice and guidelines with time".	Text amended under 2. Scope.
	For Sections 6.3.1 and 6.3.2, given the specific nature and challenges posed by studies in the adult and preschool ADHD patient population, a statement could be included that "Applicants are encouraged to seek scientific advice when planning clinical investigation in either of these patient groups".	The scientific advice procedure of EMA is considered well known by applicants. In order not to be too directive, reference to scientific advice is not provided in the guideline. Text not amended under 6.3.
	Although clinical in nature the guideline makes reference to animal studies in	

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	section 7.2 (line 290 to 294). The recommendation to investigate dependence potential in juvenile animals, an area where there is only very limited experience and very scarce scientific information and justification available about the appropriateness of animal models, appears not to be in line with current CHMP preclinical guidances. It is not clear if these recommendations have been made in collaboration with the Safety Working Party but in any case we would suggest that preclinical requirements and recommendation should not be included in clinical guidelines for the sake of consistency and the ease of reference. Should the need to make reference to animal studies in a clinical guideline be deemed necessary this should be made by cross-referencing the relevant preclinical guidelines. References in a guideline should essentially include review papers published in peer-reviewed journals summarizing scientifically robust results but not individual or almost inaccessible studies that do not allow appreciating the robustness and validity of the results. The list of references should be revised accordingly. Overall we think that this is quite a well written document and captures a number of the key aspects concerning the conduct of clinical trials in ADHD.	The text with reference to animal studies has been amended in accordance with the Safety Working Party. Review papers have been used where available.
6	We welcome this draft of the standards expected for the investigation of products for the treatment of ADHD, and are grateful for the opportunity to comment. We do so as senior European experts in the treatment of ADHD and the authors of independent European guidelines that have been influential on national policies. One general point is that (we presume) the intention of the CHMP document is to guide "registration" trials that may lead to licensing decisions; and we hope that could be emphasised so that the recommendations are not taken necessarily to refer to the later stages of pragmatic investigations.	Text amended under 2. SCOPE.
7	The guideline is well written and updated to most recent scientific evidence. We identified only 1 minor point which we feel it may be appropriate to better specify in the text.	Specific comments are provided in the referred section, starting page 49/55.
9	Regarding the age groups concerned by the draft document, i.e. children - adolescents – adults: Please specify if a paediatric indication could be pursued without an adult indication, especially as some phase I studies should only be performed in adults.	Text amended under **Methodological considerations**. With the current knowledge, a separate claim in children is a valid approach, since ADHD is considered primarily as childhood onset disorder. A separate claim in adults can only be

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		obtained either after, or in parallel with a claim in children.
10	n.a.	
11	A guideline focusing on clinical development of medicinal products for ADHD is certainly welcome. Nevertheless, this guideline tends to neglect adult ADHD. While symptoms usually start in childhood, various reviews indicate that ADHD continues into adulthood in about 30-50% of cases (Elia J. et al (1999) N. Engl. J. Med. 340 (10): 780–8). While this is eluded to in a number of places, limited guidance is provided for this age group.	See earlier comments. Text amendments have been provided to integrate the adult part of the guideline.

2. SPECIFIC COMMENTS ON TEXT

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
n.a.	1		
18	2	**Comments:** The 'focus on tasks and academic performance' should not be the only target of treatment. Behaviour and social/familial problems are frequently the main issues of concern. **Proposed change (if any):** "to be able to focus on tasks and performance" could be changed to "to be able to focus on tasks and performance, and improve associated behavioural and relational problems".	Accepted
22		**Comments:** "behavioural treatment is often provided to sustain success" is not completely right. Behavioural treatment has been shown to help the associated conduct problems of many ADHD children. **Proposed change (if any):** "behavioural treatment is often provided to modify conduct problems"	Text amended as follows: "behavioural treatment is often provided to **sustain success and to** modify conduct problems".
35-36		**Comments:** "environment that is present at the time of diagnosis" is not correctly formulated. **Proposed change (if any):** '…environment *should be* present at the time of diagnosis'.	Accepted
45		**Comments:** (bio)marker should be plural? **Proposed change (if any):** '(bio)markers'	Not accepted, original text considered correct.
40		**Comments:** It is important to reflect the fact that the ICD-10 diagnosis is more restrictive than the DSM-IV one due to the fact that ICD requires symptoms in both domains. **Proposed change (if any):** Add. "The presence of symptoms in both domains (inattention and hyperactivity/impulsivity) is necessary to qualify for an ICD-10 diagnosis. Therefore, the diagnosis is more restrictive, which makes prevalence rates different when applying ICD or DSM classifications".	Accepted
		Comments: "repeated failure in performance and the incapability of living up to expectations" is not what really	Message well taken, no text amendment necessary.

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51		differentiates both disorders, but the presence of the core symptoms of inattention/hyperactivity in both desirable and undesirable activities in ADHD	
71		**Comments:** It could be mentioned that the difference between the prevalence in clinical and epidemiological samples is due to the fact that boys are more frequently taken to the clinics because they show more aggressive behaviours.	Remark well taken. Because of lack of evidence in literature to support this statement, no text amendmends were providedno text amendment.
101		**Comments:** ICD can be noted as an alternative diagnostic manual ICD-10 should be included in parallel to DSM-IV as it is a recommended diagnostic manual in most European countries **Proposed change (if any):** latest version of DSM or ICD If EMEA plan to decline from use of ICD-10, this should be explained in text.	Accepted
104		**Comments:** diagnosis being a key basis of any ADHD study, diagnosis should remain in the hands of an experienced psychiatrist or paediatrician **Proposed change (if any):** psychiatrist or by a non-psychiatrist paediatrician experienced in ADHD and co-morbid diagnoses	Accepted. The text is a compromise to acknowledge the non-specialist, but adhere to the medical profession.
Lines 104 onwards		**Comments:** It is not specified that the psychiatrist has to be a child psychiatrist or at least to have experience of some years in working with children and adolescents. Again “a non-psychiatrist physician experienced in ADHD and co-morbid diagnoses” is not sufficiently specific; it would be necessary to ask for some specialization in psychiatric disorders in children (i.e. paediatrician with years of experience in working with psychiatric disorders in children). Many non-psychiatrists can diagnose correctly ADHD but not co-morbid disorders and they can be very confounding variables. This is a very important point as in some trials co-morbidity is not well assessed and controlled for. **Proposed change (if any):** The psychiatrist has to be a child psychiatrist or at least to have experience of some years in working with children and adolescents.	Not accepted. The proposed text is confusing, since experience is difficult to check, and will lead to unnecessary questions in the application dossier. Further, efficacy/safety should be demonstrated without confounding co-morbidity, but yet be generalized and confirmed in a phase III population that includes co-morbid conditions.

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		The "non-psychiatrist physician" has to have some specialization in psychiatric disorders in children (i.e. paediatrician with years of experience in working with psychiatric disorders in children).	
120		**Comments:** Please relate to co-morbidity of bipolar disorder (BPD) and Tourette's syndrome (TS) **Proposed change (if any):** Add a comment on BPD and TS	Not accepted. In the exclusion criteria co-morbidity, including BPD and TS, or other axis I diagnoses are excluded. There is no use of symptom rating as with mood/anxiety that relate to treatment confounding.
121		**Comments:** Information should be obtained from at least two informants (as a general quality measure in all child psychiatry). For example, child and parent or child and teacher. If you need to rule out affective disorders you necessarily need the information from the patient himself. **Proposed change (if any):** "Information should be obtained from a reliable informant (parent/caretaker/teacher)" should be changed by " information should be obtained from at least two informants"	Partially accepted. Text amended as follows: "Information should be obtained from a reliable informant (parent/caretaker/teacher), **and the child/adolescent**".
131		**Comments:** Add bipolar disorder symptoms	See comment on line 120 above.
134		**Comments:** What is the rationale for generally excluding patients with "a current or recent history of substance abuse disorder...?" **Proposed change (if any):** Especially, studies of non-stimulant drugs for treatment of ADHD could have an aim to prove efficacy and safety in patients with a history of abuse. It may have sense to narrow this exclusion criterion to studies of stimulants, or re-formulate it otherwise.	Substance abuse may mask/change symptoms and/or interfere with the investigational drug treatment. It should also be considered a general exclusion criterion for clinical trials if not in the addiction field. It is ill controlled and corrected for.
Line 159; paragraph		**Comments:** As a secondary efficacy endpoint it would be adequate to ask school grades of the last year and of the period of treatment. **Proposed change (if any):** As a secondary efficacy endpoint: school grades of the last year and of the period of treatment.	Not accepted. School grades and performance are reflected in the functional outcome measure.
167		**Comments:** Specify a Continuous Performance Task **Proposed change (if any):** Neuro(cognitive) performance	Not accepted. No specific task has been shown specific for ADHD. Therefore justified choices should be made by the investigator in relation to the investigational drug (case by

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		(especially the Continuous Performance Task).	case basis).
190		**Comments:** The duration of the study would have to be at least of 8 weeks (or even better 12 weeks) on stable dose in order to assess changes in functionality. **Proposed change (if any):** The duration of the study has to be at least of 8 weeks at stable dosage.	Not accepted. The rationale for the 6 weeks stable dose is based on data from stimulant and non-stimulant drugs.
192		**Comments:** It could be acknowledged that there is a comparator with known efficacy (methylphenidate) by emphasizing that the comparison with active comparator is mandatory and the comparison with placebo recommended.	Not accepted. A three-arm study remains the preferred design both for assay sensitivity and the fact that is allows an estimate of the new compound relative to established treatment.
249		**Comments:** Add bipolar disorder symptoms.	See earlier comments on lines 120 and 131.
300		**Comments:** Add psychosis **Proposed change (if any):** (e.g. depression, mania, psychosis, and mood)	Accepted
312		**Comments:** Relate to the issue of ECG tracing before starting treatment with psychostimulant.	No text amendment in the guideline made. ECG tracing is part of the labelling and depends on the safety outcome of the drug under investigation.
4-6	**3**	**Comments:** Suggest text is re-worded to reflect current body of knowledge regarding adult ADHD. **Proposed change (if any):** Although ADHD was originally considered a ~~disorder restricted to~~ childhood and adolescence **disorder, current evidence indicates the** signs, ~~and~~ symptoms **and impairments in some patients will** ~~may not be self-limiting,~~ **and may** ~~to~~ persist into adulthood.	Not accepted. The current text emphasizes the childhood origin, which is also the main scope and objective of the guideline.
79		**Comments:** The Company is of the opinion that the general development strategy for ADHD drugs should allow consideration of the mechanism of action of the drug. The same development strategy may not be appropriate for all investigational compounds.	Message well taken. The text reflects this issue in the way the short-term trials should be conducted (see 6.2.1).
106-107		**Comments:**, The Company does not support the proposal that separate studies must be completed for child and adolescent populations in all instances. Both populations can be	Accepted. Text amendment in section 6.2.1. 'needed in children and adolescents or at least studied I a single trial that is powered to allow analyses for the different

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		adequately studied in a single trial if the analysis for each age group is appropriately specified. Subgroup analyses would be conducted to demonstrate that treatment differences within each age group are consistent with those observed in the overall group. This position is considered to be consistent with the ICH E11 paediatric guideline that does not mandate separate studies in child and adolescent populations.	age groups'.
121-126		**Comments:** The current text of the guideline implies that in addition to physician ratings (Section 5.1), ratings by parents/caretakers **and** teachers are required when assessing children. The Company recommends that information obtained from **either** parents/caretakers **or** teachers is sufficient. It is noted that DSM-IV does not mandate teacher ratings in the diagnosis of ADHD.	Accepted. Text amended where appropriate.
135		**Comments:** The Company recommends that patients who are receiving ongoing formal behavioural, cognitive or cognitive-behavioural therapy that is not part of the study design should not necessarily be excluded from study participation in all instances. The Company suggests that these patients can be permitted provided that ongoing therapy is documented fully and controlled for within the study design. For example, if the behavioural therapy is well established and is stable prior to study entry.	Accepted. Text amended under 4.1.
151		**Comments:**. The Company does not agree that dual primary endpoints assessing symptomatic and functional domains are necessary in all instances. It is the Company's position that a study design with a single primary endpoint measuring a symptomatic response and a key secondary endpoint measuring function can result in robust efficacy assessment in the setting of practical powering requirements.	Symptom reduction and improvement in global function should be taken as dual primary endpoint to reflect the objective of pharmacotherapy.
160		**Comments:** The Company considers that ratings from physicians and trained clinical observers should also be acceptable for secondary efficacy endpoints. Consistent with comments on lines #121-126, the Company does not consider teacher ratings mandatory if physician and parent/caretaker assessments can adequately sample subject symptom improvement and functional progress, e.g., in an analogue classroom or workplace setting. Rating tasks may be	Partly accepted. Physicians should be raters for the primary endpoint. Further text amended.

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		burdensome to teachers managing a classroom and there is also the potential for privacy concerns. For example, the subject or subject's family may have concerns of revealing within the school environment that a subject is participating in a clinical study and/or has a medical condition. **Proposed change (if any):** Ratings from reliable informants (**physicians**, parent**,** ~~/~~caretaker, and/**or** teachers) should be taken as ~~primary~~ **key** secondary endpoint	
185-186		**Comments:** Please refer to the comment below (Line 193) that discusses the duration of stable dosing that is required in the clinical trials. **Proposed change (if any):** When taking methylphenidate as reference, the duration **of the stable dose period** of the trials can be short,~~ i.e. 6 weeks on stable medication, but~~ **and is** ~~the duration may very~~ dependent on the mode of action of the drug that is expected (fast or slow onset).	Not accepted. See text below (Line 193).
l93		**Comments:** The Company concurs with the guideline that the period of stable dosing should depend on the mode of action of the drug under study. However, the Company proposes that for some drugs, a period of less than 6 weeks of stable dosing maybe justified based on the onset of effect and adequate demonstration of efficacy. For example, it has been established that within the effective amphetamine dose range, the impact of stimulants on behaviour is apparent within hours of administration and that this impact is not mediated by long term changes in receptor sensitivity (Solanto MV. Neuro-psychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration Behav Brain Res. 1998; 94:127-152). **Proposed change (if any):** The duration of the ~~studies should be at least 6 weeks on~~ stable dose period of the studies **is** dependent on the mode of action of the drug.	The choice of 6 weeks on stable dose is a compromise between the use of stimulant and non-stimulant drugs, and allows for comparison between trials, irrespective of the type of drug. To build up data in this respect will contribute to the regular update of the guideline in prospective years.
194		**Comments:** Separate studies in children and adolescents is considered not necessary (see previous comment # 106-107)	Accepted. Text amended where appropriate.
221		**Comments:** The Company supports the randomised withdrawal study design to evaluate long-term maintenance of effect. However it does not support that the duration of the	Accepted. Text amended to reflect a different approach dependant on the mode of action of the study drug.

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		randomised withdrawal phase needs to be a minimum of 6 months in duration. For compounds that have an established offset of effect that is rapid, the duration of the randomised withdrawal phase could be significantly reduced (for example, 6 weeks).	
251		**Comments:** Please clarify if the guidance is recommending that the Sponsor screen subjects for depression and anxiety prior to study entry, or if depression and anxiety should be assessed during the study (or both). The Company suggests that it may not be necessary in all instances to formally assess depression and anxiety throughout the study. The need for assessment of co-morbid symptoms should be based on the co-morbid disorders allowed by protocol inclusion/exclusion criteria. Study investigators are experienced clinicians who are skilled in treating the indication in the population under study, attuned to the possibility of co-morbidities and are prepared to adequately treat any concerning symptoms. Psychiatric co-morbidities will be accurately and reliably reported in accordance with planned periodic and other interim assessments of adverse events in clinical trials.	Since the exclusion criteria state that no other axis I disorder should be present, with the exception of ODD/CD in confirmatory trials, screening for co-morbid disorders is mandatory. In addition, the presence of symptoms of depression/anxiety should be assessed in order to avoid confounding of efficacy related to the mode of action of the investigational drug. This is irrespective of a diagnosis of depression/anxiety. No text amendment.
252		**Comments:** The Company believes that the adult development program for a well-characterised paediatric ADHD product may not require additional dose-finding studies in all instances. If confirmatory studies demonstrate that adult subjects can be titrated to a tolerable and efficacious dose in a timely manner and that the upper dose is not limiting, then separate adult dose-ranging studies are not needed.	Remark well taken. Since ADHD symptoms may change over time from childhood to adolescence to adulthood, dose finding may be appropriate for all different populations. Whether a full program is needed depends on the drug under investigation and should be justified by the investigator.
314		**Comments:** The pharmacological profile of the investigational product should determine the endocrinological adverse reactions (specifically disturbance in libido) that should be assessed. **Proposed change (if any)** ~~In adolescents and adults,~~ Depending on the pharmacological profile, disturbance in libido should be assessed **in adolescents and adults when appropriate**.	Accepted. Text amended.
59 ff	**4**	**Comments:** Co-morbidity may have an influence on the outcome of pharmacotherapy. More data is needed on the	Comorbidity is taken care of by allowing certain co-morbidity in confirmatory trials, but not the phase II dose finding/proof

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		efficacy of various drugs considering a different spectrum of co-morbidities. **Proposed change (if any):** amendment necessary	of principle studies. No text amendment needed.
282 ff		**Comments:** Atomoxetin may have hepatotoxic effects **Proposed change (if any):** amendment necessary	The guideline should not refer to specific safety issues of particular drugs. Hepatotoxicity is part of the routine safety screening as reflected in the ICH E1 guidance.
295 ff		**Comments:** A statement is missing that stimulants at higher doses may lead to agitation and elevated excitability. Moreover there is a decrement of the seizure threshold. **Proposed change (if any):** amendment necessary	Text is amended under 7.2.2.
Line 4-6	**5**	The statement: "*Although primarily a disorder restricted to childhood and adolescence, signs and symptoms may not be self-limiting but to persist into adulthood*" is inconsistent and under represents the persistence of disorder in adulthood, generally thought to occur in at least 2/3 of cases **Proposed change (if any):** The revised statement should be: "*Although primarily a disorder **diagnosed in** childhood and adolescence, signs and symptoms may not be self-limiting but ~~to~~ persist into adulthood*."	Accepted, text amended.
Line 7-8		**Comments:** This guideline is intended to provide guidance on the evaluation of new medicinal products in ADHD with focus on the childhood onset': In accordance with DSM IV, ADHD onset is always at childhood (even if symptoms are detected for the first time during adulthood). However, clinical development programs should also take into account adult ADHD. **Proposed change (if any):** The revised statement should be:: …….*evaluation of new medicinal products in ADHD with focus on the childhood onset ~~onset~~ **manifestation of symptoms** **and long term management in adults**.*	Partially accepted. It is the opinion of CHMP to keep the focus of the guideline on ADHD as a child psychiatric disorder. Yet the persistence of symptoms into adulthood will not be ignored, but data are lacking to substantiate that this is the case in the majority of patients as suggested by the company. Therefore, the text will be amended as follows: 'with the main focus on the childhood onset, yet not denying manifestation of symptoms in adults.
Line 22-24		**Comments:** Regarding *"Within this context, cognitive treatment, neurofeedback training and dietary measures can be regarded as potential, but not yet evidence based strategies."* Non-pharmacological approaches such as dietary measures should not be described as "within the context" of "psycho education," whether alone or together with	Accepted

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		pharmacotherapy. **Proposed change (if any):** We propose to rephrase as follows: *In the context of non-pharmacological interventions, cognitive treatment, neurofeedback training and dietary measures can be regarded as potential, but not yet evidence based strategies.*	
Line 25		**Comments:** As the document discusses also ADHD in adults, the sentence "*It has long been acknowledged that the core symptoms of ADHD ameliorate with age*" is not accurate. **Proposed change (if any):** The revised sentence should read: "*It has long been ~~acknowledged~~ **assumed** that the core symptoms of ADHD ameliorate with age*"	Accepted
Line 25-26		**Comments:** Regarding "*It has recently been recognized that symptoms may persist into adulthood*,". Both symptoms of ADHD as well as impairment in social or occupational functioning may persist into adulthood. As symptom criteria and impairment criteria are distinct entities (albeit potentially overlapping) and given the increased focus on improving both symptoms and functional outcomes, we suggest clarification of the above sentence. **Proposed change (if any):** *It has recently been recognized that symptoms **and impairments** may persist into adulthood.*	Accepted
Line 28-29		**Comments:** Regarding: "*… thereby emphasizing the need for long term safety data in an otherwise healthy patient group."* As ADHD is frequently comorbid with psychiatric and other disorders, this sentence should be clarified to capture both patients with comorbidities as well as otherwise healthy patients. **Proposed change (if any):** *"As ADHD is a chronic disorder, long term treatment can be foreseen, thereby emphasizing the need for long term safety data in a group of patients that does include many otherwise healthy individuals".*	Accepted
Line 31-45		**Comments:** Adult ADHD presents itself differently from child ADHD **Proposed change (if any):** A description of adult ADHD and	Text amended according to text under 6.3. Cave: it should be kept in mind that the guideline's focus is on the childhood origin of ADHD. No new diagnostic criteria for

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		diagnosis should be provided	adult ADHD can be expected from this guideline as the DSM is taken as leading to a proper diagnosis.
Line 31		**Comments:** As there are cases in which a diagnosis of ADHD is not made until the patient is an adult, the statement "ADHD first comes to attention in children and adolescents" should be modified. **Proposed change (if any):** "ADHD usually first comes to attention in children ~~and adolescents~~,…"	Accepted
Line 33		**Comments:** DSM IV criteria focus on child ADHD and are not very suitable for diagnosis in adults. How reliable is the retrospective assessment of the symptom descriptions and diagnostic criteria for adults that refer to the situation before the 7th year of life? We believe that in the diagnosis of adult ADHD, the experts are more likely to go back no further than the 12th year of life, when retrospectively questioning adults. See also comment in Line 248 **Proposed change (if any):** A recommendation for a suitable diagnostic tool for adult ADHD should be provided.	Not accepted. So far no other valid diagnostic tools such as DSM or ICD are available. Diagnostic validity should be justified by the investigator. Otherwise, the text is amended for 'verifiable presence of symptoms at young age'.
Line 39		**Comments:** More details on ADHD subtypes also considering adulthood should be provided. See also comment in Line 60 – 63. **Proposed change (if any):** The relative prevalence for each subtype should be provided. For example, the combined type is more commonly seen in health centres, whereas ADHD-HI is hardly seen. Children with ADHD-IA are much harder to find, since the associated symptoms lead less quickly to behavioural problems and therefore less referrals to health centres. While hyperactivity is common in children with ADHD, it tends to disappear in adulthood. In contrast, half of the ADHD children continue to have attention difficulties in adulthood.	There is insufficient reliable data in the public domain to get further into detail on the specific subtypes. Text not amended.
Line 40		**Comments:** ICD-10 classification is mentioned here, but no where else in the guideline. **Proposed change (if any):** Greater explanation should be provided on when and how to use ICD-10, especially because the ICD-10 criteria differ significantly in terms of severity to the DSM-IV criteria.	Text amended.
Line 46-58 and 99		**Comments:** Differential Diagnosis and Inclusion Criteria – Largely based on DSM-IV-TR criteria, but revisions are	Partially accepted. Text amended under 2.

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		currently underway for DSM-V and discussions include modification or elimination of some of the criteria in this section, including onset prior to age 7 and exclusion of PDD. This section should reference more generally to accepted diagnostic criteria to avoid conflict with updated diagnostic criteria.	
Line 48		**Comments:** ADHD comorbidity may also occur in highly intelligent children. This is a special group, in which still relatively little research has been done.	Message well taken, no text amendment needed.
Line 50-55		**Comments:** It is stated that ADHD should be discriminated from oppositional behaviour due to repeated failure in performance and the incapability of living up to expectations. We question whether such criteria adequately discriminate ADHD from Oppositional Defiant Disorder or Conduct Disorder. The differential diagnosis of ADHD, Oppositional Defiant- and Conduct Disorder and Stereotypic Movement Disorder is complex and multifaceted. Reducing the differentiating features to a single sentence ("*due to repeated failure in performance and the incapability of living up to expectations*"[…]" *hyperactivity is more focussed to specific body parts*") does not help clarify these differences between disorders and is not necessary to the scope of the guideline. **Proposed change (if any):** Guidance could include limiting the description differential diagnosis listing for ADHD, possibly citing DSM-IV differential diagnosis.	Text not amended. For pragmatic reasons, the text as originally proposed will be kept. To incorporate the DSM-IV differential diagnosis section would be disproportionate to the other parts of the guideline
Line 54		**Comments:** The following statement do not add clarity: *"…., e.g. mood and anxiety, and personality disorders. In specific bipolar disorder in children should not be mixed up with ADHD.*" **Proposed change (if any):** We suggest to delete *"…. e.g. mood and anxiety, and personality disorders. In specific bipolar disorder in children should not be mixed up with ADHD.*"	Not accepted. Mood and anxiety may present with inattention and other symptoms of ADHD.
Line 57-58		**Comments:** Regarding "*ADHD should not be diagnosed if symptoms present in the context of a pervasive developmental- or psychotic disorder*." Clinical practice on this point is evolving, as reflected in the changes between DSM-III, DSM-IV and potentially the upcoming DSM-V in this regard.	See earlier comment on lines 50-55.

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		Proposed change (if any): If guidance is limited to a differential diagnosis (see comment on lines 50-55 above) rather than specifying diagnosis criteria for a range of disorders, the proposed guideline will continue to be of relevance when clinical practice and criteria evolve (such as the imminent update of DSM-IV to DSM-V).	
Line 60 - 63		**Comments:** We propose to break down by subtypes and provide the relative prevalence for each subtype. ~~See also comment in Line 39.~~	Not accepted, see earlier comment on line 39.
Line 63 - 64		**Comments:** The Finish Cohort Study quoted might not have been representative. We think that the combined type is the most prevalent group.	The reference has been deleted.
Line 71		**Proposed change (if any):** Add the following sentence at the end of the paragraph: " In older adolescents, the ratio of male-to-female ADHD is approximately 1:1, while among young adults ADHD is about 2-fold more predominant in women." Reference: (Dulcan M (1997) *J Am Acad Child Adolesc Psychiatry* **36 (**10 Suppl) 85S–121S).	Data are insufficient to incorporate such statement in the guidance document at present.
Line 73		**Comments:** Besides co-morbidity with ODD and CD, learning disorders / disabilities seem to occur at least as often (Kroes M (2001) *J Am Acad Child Adolesc Psychiatry* **40**: 12, 1401S-1409S). Therefore, is the choice for inclusion of co-morbidity with only ODD / CD sufficiently justified? See also comment in Line 112 and 129-130.	There are insufficient data to accept other co-morbidities in the clinical trials. The text remains as it is. ~~Leave text as it is.~~
Line 76		**Comments:** Co-morbidities need to be taken into consideration when conducting clinical trials. **Proposed change (if any):** Change the sentence: "In older subjects, substance abuse is often found to be morbid" with "In adult ADHD, co-morbidities can include depression, anxiety, bipolar disorder, learning difficulties and substance abuse."	Text for adults will be amended.
Line 83-97		**Comments:** The ad hoc group for the development of implementing guidelines for Directive 2001/20/EC has drawn up recent recommendations on various ethical aspects of clinical trials performed on children. Given the relevance of these recommendations to all paediatric clinical trials, we suggest this document is included in the list of reference guidelines and regulations.	Accepted

Line No.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		Proposed change (if any): We suggest inclusion to include the following document to the reference list: "Ethical considerations for clinical trials on medicinal products conducted with the paediatric population" (Recommendations of the Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use).	
Line 98		**Comments:** Section 4 refers almost exclusively to a child and adolescent population. The exception to this is line 132 (see later comment), which contains a reference to a specific adult diagnosis. Given that specific sections of the guideline are devoted to adults (6.3.1) and pre-school children (6.3.2), the title of this section could more accurately reflect the diagnostic information relevant to the child and adolescent population contained within. **Proposed change (if any):** Change the tile of Section 4 to read: ***"PATIENTS CHARACTERISTICS AND SELECTION OF CHILD AND ADOLESCENT PATIENTS"***	Text integrated in amended version of the guideline.
Line 100-101		**Comments:** DSM IV criteria focus on child ADHD and are not very suitable for diagnosis in adults. ~~See also comment in Line 33.~~ **Proposed change (if any):** A recommendation for a suitable diagnostic tool for adult ADHD should be provided.	See earlier comment (line 33).
Line 101-102		**Comments:** Regarding: *The inclusion of subtypes should be specified.* (1) In order to reflect the recommendation of the previous sentence that "the latest version of the DSM" is used, and as definition of subtypes evolves between different versions of DSM criteria, this sentence could be clarified as suggested. **Proposed change (if any):** *Assessment of subtypes should be carried out according version of the DSM current when the study is conducted.*	Accepted
Line 102-103		**Comments:** Regarding: *The use of a severity rating scale or cognitive performance task is additional, but should not replace a clinical diagnosis.* Rewording could clarify that clinical assessment is the primary	Accepted

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		basis for diagnosis, but should be supplemented by a severity rating scale or cognitive performance task. **Proposed change (if any):** *Diagnosis should be based on clinical assessment, but should be supplemented by a severity rating scale or cognitive performance task.*	
Line 103-105		**Comments:** The statement "*Diagnosis should be made by a psychiatrist or by a non–psychiatrist physician experienced in ADHD and co-morbid diagnoses, and who is trained in the use of structured interviews to confirm the diagnosis and exclude relevant co-morbid disorders*." implies that only an experienced psychiatrist or trained non-psychiatrist physicians may make a diagnosis of ADHD. While this may be current practice in the EU, regions outside the EU may not reflect this practice and clinical psychologists with appropriate training and experience with ADHD also commonly diagnose patients. The proposed condition may unnecessarily limit the value of ex-EU studies (e.g. US studies) in a dossier submitted to EU authorities. Clinicians who confirm the diagnosis and act as raters in clinical trials are not necessarily "physicians"; i.e. they do not necessarily hold a medical degree but may be licensed as clinical psychologist and meet guidelines for clinical expertise required to make a diagnosis and rate in clinical trials. **Proposed change (if any):** If this statement is incorporated in the guideline, it should be re-phrased as follows: "Diagnosis should be made by a psychiatrist, **clinical psychologist** or by a non–psychiatrist physician experienced in ADHD and co-morbid diagnoses, and who is trained in the use of structured interviews to confirm the diagnosis and exclude relevant co-morbid disorders."	Not accepted, the guideline predominantly reflects the EU situation. All deviations should be justified, but not be a priori a reason for text revision.
Line 106-107		**Comments:** It is a unclear whether the two age groups can be in the same study or whether separate studies are preferred. Assessing relative efficacy in the two groups (children and adolescents) is a key consideration. Therefore, guidance should amplify on the above statement. It is stated on page 3 that 'It has recently been recognised that symptoms may persist into adulthood, thereby extending treatment to this age.' It is further acknowledged that the	Text has been amended accordingly.

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		guideline focuses on childhood manifestation of symptoms. Nevertheless, adult treatment may be necessary and the upper age restriction of 18 years does not seem justified and requires further clarification. Is extrapolation acceptable? **Proposed change (if any):** We suggest to rephrase the sentence to read: *"In order to assess relative efficacy in the different age groups, children and adolescents can either be studied in separate studies, or, if both populations are included in a single study, analyses should then be stratified according to age.*	
Line 108-109		**Comments:** Dose finding in a population with ADHD only aims to provide as clear an interpretation of efficacy in treatment of ADHD (not comorbidities) as possible. However, there are a number of issues with this recommendation: 1) The proposed guideline goes on to state that inclusion of subjects with co-morbidities is acceptable in confirmatory studies. The dose-finding study (ADHD only) would therefore have been carried out in a different population to that included in confirmatory studies (ADHD and co-morbidities), necessitating the assumption that the dose identified in the ADHD-only population was also applicable to the ADHD and comorbidities population. 2) Most patients with ADHD and no significant comorbidities are likely to been treated with stimulant medication as first- line therapy. Therefore, a patient population with ADHD only recruited to a dose finding study is likely to be biased by inclusion of patients who are non- or poor responders to stimulant treatment. The patients most likely to be treated with novel therapeutic agents in the clinical setting are patients with co morbidities, not patients with ADHD only, who are likely to receive stimulant medication. The study population should therefore reflect the expected clinical population even at the dose finding stage. **Proposed change (if any):** Guidelines could include discussion around inclusion of patients with ADHD only, as well as patients with co morbidities in dose finding studies, together with a recommendation that comparison between the two	Not accepted. Although the comments made are considered correct, the strategy chosen is regarded most efficient, thereby not over asking data in children, yet allowing assessment of the true efficacy on the core symptoms of the disorder to be balanced against some inflation in the real world population. It is up to the treating physician to adjust treatment to the individual patient. Text not amended.

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		subgroups are carried out as part of the analysis to identify any differences in response between the two groups.	
Line 111-113		**Comments:** ODD/CD: Abbreviation is not defined. ODD/CD is not the only co-morbid diagnosis. Does the statement: 'In confirmatory trials, the inclusion of subjects with ADHD and co-morbid ODD/CD is acceptable as it enables generalization…' apply to all types of co-morbidity? **Proposed change (if any):** We suggest that the abbreviation [Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD)] be used in line 50 section 1.2 The statement should be read: 'In confirmatory trials, the inclusion of subjects with ADHD and co-morbid **conditions such as** ODD/CD is acceptable as it enables generalization…'	Accepted
Line 114		**Comments:** The guideline should contain a general statement to ensure that diagnostic criteria current at the time of study development are taken into account. **Proposed change (if any):** *Patient characteristics should be based on current and emerging diagnostic criteria.*	Accepted. Text amended under 2. SCOPE.
Line 119-120		**Comments:** Recommends rating co morbid symptoms such as depression, anxiety with proper scales, but this is difficult to interpret since above (110-111), recommendation is to exclude subjects with co morbid conditions. Are existing rating scales sensitive enough to change and validated for monitoring the severity of psychiatric symptoms in a population specifically designed to exclude subjects with diagnosable psychiatric disorders? Would AE reporting be a better way (or at least complementary way) to monitor the effect of the pharmacotherapy in this population without psychiatric co morbidities? **Proposed change (if any):** Reference to relevant guidelines should be added with respect to proper scales	Reference is made to the specific guidelines on depression and anxiety disorders in the text under 'Diagnosis and Inclusion Criteria'. The suggestion for rating depressive and anxiety symptoms as adverse events is not supported. There is a need for monitoring the symptoms during treatment, because of the potential confounding of specific drugs.
Line 126		**Comments:** 'In case of adolescents, the teacher ratings are not mandatory' Would this not introduce variability in data collection? **Proposed change (if any):** Add: In the case of adolescents, the teacher ratings are not mandatory **but recommended.**	Accepted. Self report becomes more relevant in this age group.

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Line 129-130		**Comments:** The exclusion criterion, "another Axis I disorder (co-morbidity) with the exception of ODD/CD (as mentioned for confirmatory trials), albeit that ADHD should be the primary diagnosis" should be revised. Subjects with a lifetime diagnosis of relevant comorbid Axis I psychiatric disorders, which are currently asymptomatic and clinically stable for the comorbid condition should not be excluded. Given how common these co-morbidities are with ADHD, this exclusion could limit enrolment and decrease the ability to generalize the findings to a broader patient population. **Proposed change (if any):** If this statement is incorporated in the guideline, it should be re-phrased as follows: "***Current diagnosis of*** *another Axis I disorder (co-morbidity) with the exception of ODD/CD (as mentioned for confirmatory trials), albeit that ADHD should be the primary diagnosis*"	Text amended as follows: "***Current diagnosis of*** *another Axis I disorder (co-morbidity)*, ***i.e. within 6 months prior to inclusion….****".*
Line 131		**Comments:** The exclusion criteria pertaining to "severe co-morbid symptoms…" is vague, overly broad, and insensitive to development of emotional regulation across the affected age range **Proposed change (if any):** Delete "severe co-morbid symptoms such as anxiety, depression"	Not accepted. The text refers to situations where overt anxiety/depressive symptoms are present without reaching the full Axis I diagnosis
Line 132		**Comments:** Exclusion criterion: 'a primary Axis II disorder (personality disorder in the case of adult diagnosis)' The addition in brackets suggests that the guidance does take into account the possibility of adult diagnosis of symptoms. This seems contradictory with earlier restriction of the upper age for studies and should be clarified.	Text for adults is integrated in the amended version of the guideline
Line 132		**Comments:** The exclusion criterion, "a primary Axis II disorder (personality disorder in the case of adult diagnosis)" should be revised. Section 6.3.1 indicates that borderline- and antisocial personality disorders are common comorbidities in adult patients with ADHD (Lines 248-249), and furthermore suggests allowing enrolment of subjects with predominant comorbidities to enable generalization of the study results to the target population (Lines 254-255). The relevant exclusion	Not accepted. The adult section should follow as close as possible the strategy followed in children/adolescents for reasons of diagnostic and treatment validity.

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		criterion should be revised to allow enrolment of these subjects. **Proposed change (if any):** If this statement is incorporated in the guideline, it should be re-phrased as follows: "*A primary Axis II disorder **(other than borderline- and antisocial** personality disorder in the case of adult diagnosis)*"	
Line 133		**Comments:** A separate exclusion criterion for mental retardation is unnecessary if exclusion of a primary Axis II disorder is respected (see line 132) **Proposed change (if any):** Change Line 132 to read: "a primary Axis II disorder (mental retardation or personality disorder in the case of adult diagnosis)"	Text amended as follows: "a primary Axis II disorder, **including mental retardation…..**".
Line 135-136		**Comments:** The statement, "Ongoing formal behavioural, cognitive or cognitive-behavioural therapy that is not part of the study design" should be revised. Behavioral therapy is a part of the holistic approach to treating patients with ADHD and is often part of the treatment program provided to children and their families. We agree that the inclusion of patients who have recently initiated or undergone a change in the frequency of sessions of behavioral or cognitive behavioral therapy would be a potential confound. However, if a patient has been receiving behavior or cognitive behavioral therapy for ≥ than 3 months and the frequency of sessions has not changed, we would argue that the therapy was stable and would not be a confounding factor. We suggest the exclusion criterion be revised to indicate that patients should not start, or in the case of those receiving therapy, should not change the frequency of sessions of, behavioural therapy within 3 months of study enrolment or during the clinical study. **Proposed change (if any):** If this statement is incorporated in the guideline, it should be re-phrased as follows: "***Newly initiated** formal behavioural, cognitive or cognitive-behavioural therapy **or change in frequency of sessions within the prior 3 months or during the course of the study,** that is not part of the study design"*	Text amended, with the inclusion of the statement that stratification in the treatment design is necessary.
Line 137-138		**Comments:** The most common on-going psychotropic co-medication will be methylphenidate. For consistent practice	Text amended, but in a more general way to allow other treatments as well.

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		between trials, should not a minimum washout period be stated. Also long lasting receptor changes should be considered. **Proposed change (if any):** Add….In the case of methylphenidate, a washout period of **X** days should be applied.	
Line 137		**Comments:** Exclusion criterion: 'ongoing relevant psychotropic co-medication for ADHD' Please add "indicated". **Proposed change (if any):** Exclusion criterion: 'ongoing relevant psychotropic co-medication **indicated** for ADHD'	Accepted
Line 139-140		**Comments:** The statement "Relevant somatic/neurological disorders that exclude participation because of the pharmacology of the study drug (e.g. epilepsy)" should be revised to exclude Tic disorders unless it is believed that specific mechanism of action of the drug may worsen existing symptoms. "Tic disorder" was recently deleted as a contraindication from the Core SmPC of methylphenidate-containing medicinal products in the EU. Tic disorder is a common co-morbid condition in children with ADHD. Placebo-controlled studies have shown a beneficial effect of stimulant medications on ADHD symptoms and co morbid Tic disorder in affected children. While this therapeutic effect may not apply to medicines of other therapeutic classes, the inclusion criteria of studies in children with ADHD should allow for the systematic evaluation of the effect of an investigational product on comorbid Tic disorder. Consideration should be given to the use of a relevant assessment tool if studies are aimed at establishing a therapeutic benefit in co morbid Tic disorder. **Proposed change (if any):**If this statement is incorporated in the guideline, it should be re-phrased as follows: "*Relevant somatic/neurological disorders* ***(other than Tic disorder)*** *that exclude participation because of the pharmacology of the study drug (e.g. epilepsy)".*	Not accepted. There are insufficient data to accept Tic Disorder as a common co morbid condition. If additional benefit of products are to be demonstrated on co morbid Tic Disorder, this should be justified in the investigation protocol.
Line 143-158		**Comments:** Mention should be given to various types of possible study designs (such as outpatient studies in which scales such as the ADHD-SRS scale would be primarily used and laboratory classroom studies in which symptoms of ADHD	Partially accepted. Laboratory classroom studies are considered proof of concept studies. The text is amended under 6.1.1 Pharmacodynamics: …. ADHD symptoms 'e.g. in a laboratory classroom setting. In these studies time to onset

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		could be evaluated by school teachers and observers using the deportment subscale from the Swanson, Kotkin, Agler, M-Flynn, and Pelham [SKAMP] rating scale). Additionally, the criteria to obtain "time to onset" and "time to offset" should be defined such that patients (parents monitoring their children, for example) can decide when to take the drug in order to secure maximum benefit for the challenges present in their day. **Proposed change (if any):** Add "A combination of clinical study designs can be used to secure product approval, as outpatient studies secure different types of information and use different rating scales than laboratory classroom studies. Time to onset and time of offset are also better captured using laboratory classroom studies in which symptoms of ADHD can be evaluated by school teachers and observers using the deportment subscale from the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale."	and time to offset can also be captured.
Line 143-144		**Comments:** Regarding: *"the most prominent being the Connors' Rating Scales."* Is the Conner's rating scale valid for all ages (in terms of validity / reliability)? As there are a number of different versions and subscales of the Conners scales (see for example http://www.mhs.com/conners/; Iowa Conners), guidance should include further information as which versions are most useful.	Spelling corrected. No recommendation will be provided regarding versions of scales, which is up to the responsibility of the Company.
Line 145		**Comments:** We propose to also consider semi-structure interviews (e.g. Dica for children), when the clinician can also ask about other psychiatric problems	Accepted. Text amended under 4.1.
Line 147-150 & 160-161		**Comments:** Regarding: '*Observer' scales, assessed by clinicians should be taken as primary*' The guideline proposes that "observer" scales ("assessed by clinicians") are the basis of the primary efficacy endpoint, while ratings from informants (parent/teacher) are the basis of the secondary endpoint (line 160/161). However, the ADHDRS-IV is administered and scored by the clinician, based on an interview with the parent or teacher. It is not clear whether this would be considered a primary or secondary endpoint.	Text amended as follows: '*Observer' scales, assessed by clinicians**, with the help of reliable informants (parents/caretakers or teachers,** should be taken as primary*' No reference will be made to specific scales for quality of life. The choice is up to the investigator and should be justified accordingly.

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		We suggest to also specify the role of the parents in evaluation of improvement **Proposed change (if any):** Use of a citation in both instances would ensure clarity around the preferred scale. For example, :'*Observer' scales, assessed by clinicians (such as : ADHD rating Scale-IV: Checklists, Norms and Clinical Interpretation by George J. DuPaul, Thomas J. Power, Arthur D. Anastopoulos, and Robert Reid, 1998, page 70 and 74) should be taken as primary'* Add also a reference to Jeanne M. Landgraf AIM scales developed for evaluation of quality of life.	
148-158		**Comments:** It is not clear why 2 primary endpoints are required. In ADHD there is no real separation between behaviors, function and QOL and behavioral modification is the goal of treatment of ADHD. The ADHD core symptom rating scales measure function in a basic sense. A second primary efficacy endpoint for function will impact on the sizing of trials and the ethics of recruiting children into large studies. If measures of function are to be included we believe it is more appropriate to view them as secondary endpoints. However a clear definition of what functional outcomes should be measured would be helpful and how they differ from QOL measures. Functional deficit in ADHD can also be described as neurocognitive (executive dysfunction), and more contextual dysfunction (school/work/social). More specificity would be valuable. Emphasis is placed on a clinician rated severity scale but we question whether this is enough or does it need reference to a self/peer rated scale too? (such as is the original instruction for CAAARS-O to be used in conjunction with CAARS-S?	Symptom reduction and improvement in functioning is the primary objective of pharmacotherapy.
Line 151		**Comments:** Regarding "Two primary endpoints should be stipulated reflecting the symptomatic and the functional domain." Assessment of functional outcome as well as symptom reduction is crucial, and we agree that both should be assessed. However, there are several concerns with elevating a functional outcome to a co-primary endpoint: 1) clinical relevance is assessed directly by improvement	Functional outcome is regarded essential for future trials in ADHD, since improved functioning at the school performance and social level is considered the ultimate treatment goal. Since functional improvement in school/social performance is difficult to change in 6 weeks time, this measure has been made secondary. Symptom reduction and improvement in global functioning should be taken as co-primary endpoints.

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		in ADHD symptoms, whereas functioning may improve for reasons not only related to ADHD improvement 2) A number of studies indicate only a small to moderate correlation between symptoms and functional outcomes in ADHD, raising concerns over a dual primary endpoint that includes both a specific symptomatic outcome together with a more diverse functional outcome that is not necessarily related to the primary symptomatic improvement. 3) Sample size is likely to need to increase in order to successfully meet co-primary endpoints having weak correlation. This may result in huge/non feasible sample sizes, especially the case where some of the allowed co-primary endpoints may be "experimental". 4) It is not clear which functional scales should be used, what the scale should specifically investigate, and in which social setting (i.e. school performance or social functioning or both). 5) It is not clear that the 6 week study duration recommended for short-term trials is long enough to consistently detect functional improvement across different domains. Evidence of clinical relevance beyond purely symptomatic improvement is being requested. However, the ADHD-RS assessment already directly assesses important outcomes such as concentration. **Proposed change (if any):** The guideline could stipulate that functional outcomes must be tested as a secondary endpoint and that the direction of functional endpoint results must be consistent with the direction of symptomatic outcome results, to show consistency of response. Guidelines on appropriate functional outcomes could be given. The importance of using scales that assess functional outcome across different environments (such as the Child Health and Illness Profile Child and Adolescent Editions (CHIP-CE and –AE)) should be emphasized.	
Line 151		**Comments:** The statement, *"Two primary endpoints should be stipulated reflecting the symptomatic and the functional domain."* indicates that two primary endpoints that meet	Not accepted. Claims should be targeted for treatment of ADHD. This requires both symptom and functional improvement expressed in a co-primary endpoint. There is no need for multiplicity since both measures reflect different

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		statistical significance adjusted for multiple comparison have to be met for an approval of a symptomatic therapy in ADHD. Determining statistical significance in a functional outcome measure during a six-week trial may be difficult. We agree that functional outcome is an important secondary endpoint for this patient population, however unlike ADHD symptoms in short term trials, one would not necessarily expect to see improved functional outcomes as early as 6 weeks, particularly with the adult population. Unlike the paediatric population where assessment in a laboratory school setting may give an early indication of the impact of symptomatic improvement in ADHD symptoms on academic performance as a functional outcome, there are no equivalent measures to the lab based measures of performance for adults. In adults, while there are some patient reported outcomes instruments which assess functional domains, it is not clear that behaviours associated within multiple domains can reasonably be expected to detect change during the course of a short-term clinical trial. Functional improvements are a measure of treatment benefit on patients' function in everyday life, and therefore, pre-specified functional domains may be most effectively used as a secondary measure to support a primary endpoint. Even though, potential impact on aspects of daily functioning may not be ascertained in short-term trials, these measures are an important outcome. In addition, the clinical relevance of changes in the primary endpoint evaluating an improvement in ADHD symptoms will be illustrated by a number of other secondary endpoints (e.g. responder analysis with "clinical response" defined on the basis of the relevant ADHD symptom rating scale score, change in a global outcome measure such as CGI). The symptom rating scales that are commonly used to provide the primary endpoint in clinical trials of ADHD are comprehensive and cover relevant domains in addition to cognitive function. This obviates the need for a co-primary endpoint defined on the basis of a functional outcome measure to confirm the clinical relevance of an improvement in ADHD symptoms. The selection of the total score on a validated ADHD symptom	aspects of the disorder. Therefore the primary efficacy should be defined by two primary endpoints, i.e. reduction of symptoms and improvement in global function.

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		rating scale as a single primary variable in confirmatory trials in ADHD reflects the accepted norms and standards in the field of clinical research in psychiatry. There is sufficient published evidence in supporting that such a primary variable can provide a valid and reliable measure of a clinically relevant and important treatment benefit in the patient population described by the inclusion and exclusion criteria of confirmatory trials in ADHD. **Proposed change (if any):** If this statement is incorporated in the guideline, it should be re-phrased as follows: "***One*** *primary endpoint should be stipulated reflecting the symptomatic domain".*	

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Line 154-155		**Comments:** The statement, "The use of the same rating scale for inclusion, efficacy and responder definition is recommended" should be deleted from the document to allow for more flexibility. Given the growing problem of high placebo response in clinical trials in psychiatry, some recent clinical trials have used a different rating scale for inclusion than the primary outcome measure (for efficacy and response). While use of the same (primary) rating scale may be used at the Screening and Baseline, we would like to leave the option open of making enrolment in the study dependent on the score on another rating scale to prevent potential rater inflation for the primary endpoint. We would suggest to leave open the option to use different scales if scientifically justified. **Proposed change (if any):** If this statement is incorporated in the guideline, it should be re-phrased as follows: "*The use of the same rating scale for efficacy, and responder definition is recommended but different scales may be used if scientifically justified"*	Not accepted. Placebo response is no reason for choosing different assessment instruments for inclusion and efficacy/response. By using the same rating scales throughout the study, data are easier to interpret, despite some rater inflation. Deviation from this recommendation should be justified by the investigator.
Line 157-158		**Comments:** The statement, "*Methods should be foreseen in the study protocol to assess inter-rater reliability*," should be revised to delete reference to the protocol as this information generally is included in separately produced rater training manuals rather than in the protocol. When the protocols of confirmatory trials in ADHD are being finalized, the precise nature of rater training and qualification has often not yet been agreed. This is commonly done in consultation with vendors on the basis of a final protocol. Consequently, the method for the assessment of inter-rater reliability is agreed and is documented separately. To allow for this flexibility, the method for the assessment of inter-rater reliability should not be pre-specified in the protocol. **Proposed change (if any):** If this statement is incorporated in the guideline, it should be re-phrased as follows: "*Methods should be foreseen to assess inter-rater reliability"*.	Accepted
Line 160-161		**Comments:** The term "primary secondary" is potentially confusing.	Accepted

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		Proposed change (if any): Replace "primary" by "main" or "key" secondary endpoints.	
Line 163-164		**Comments:** It is not clear what "see II.I" refers to, please clarify.	Deleted
Line 175-181		**Comments:** The FDA guidance specifically recommends that PK, safety and tolerability data be generated in adult population when disease under investigation is present in both children and adults in similar forms, but this extra aspect of safety monitoring for a vulnerable paediatric population is not discussed in the guidance	Text amended under 6.1.2. However, it should be kept in mind that the present guideline takes a EU perspective. Therefore, the focus is on ADHD as childhood onset disorder, where symptoms may persist into adulthood.
Line 176-177		**Comments:** The statement "*Pharmacokinetic studies should be performed for each age cohort separately*," should be revised to indicate that relevant studies are only meant to characterize the pharmacokinetic profile in each age cohort separately. The studies required for each age category separately are only meant to characterize the pharmacokinetic profile in that age category. Obviously, there is no need for a full PK package in each of the age categories separately. Further additional PK studies, including bioequivalence, dose-proportionality, food effect studies, potential drug-drug interaction, and assessment of the effects of renal and hepatic impairment will commonly be conducted in adult subjects only. **Proposed change (if any):** If this statement is incorporated in the guideline, it should be rephrased as follows: "***Studies should be performed to characterize the pharmacokinetics of the compound*** *for each age cohort separately."*	Accepted. Text amended under 6.1.2.
Line 180-181		**Comments:** As it is likely that ADHD patients will have been treated with stimulants, these should be specifically mentioned in the drug interactions section. **Proposed change (if any):** *Special interest should bet taken in interactions with stimulation medication as well as alcohol and other CNS active products, which are relevant from a safety perspective.*	Accepted
Line 183-185		**Comments:** The statement "Randomized, controlled, parallel fixed dose studies, using at least 3 dosages are needed to	Partially accepted to allow for some flexibility in the choice of design: **"***As far as possible the lower end of the clinically*

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		establish as far as possible the lower end of the clinical effective dose range as well as the optimal dose. Generally it is recommended to add a placebo arm as well as an active comparator" should be revised based on the following: • Randomized, controlled, parallel fixed dose design is one approach. However, there are other acceptable study designs for establishing optimal dose, such as crossover design, which has been successfully utilized in studies with methylphenidate. Studies with a randomized crossover design may be adequate to evaluate the dose response for compounds with a relatively short elimination half-life. Revision of this statement as requested would allow for other study designs that may inform the selection of doses to be evaluated in confirmatory studies as per the ICH E4 Guideline. As placebo and/or an active comparator are only meant to establish assay sensitivity, the inclusion of either treatment in a dose-response study should be optional. The text as written may be interpreted~~,~~ as meaning that separate dose response studies using at least 3 dosages are required in each age cohort. There should be flexibility in the approach taken in determining dose response depending on the PK characteristics of the drug. For example, where the PK characteristics are similar across the various age groups, it may be appropriate to either conduct dose ranging studies in a combined paediatric population or to conduct a dose ranging study in one age cohort and extrapolate the findings to the other age cohort (e.g. adjusting for differences in body weight). We have proposed a sentence to provide clarification on this point. **Proposed change (if any):** If this statement is incorporated in the guideline, it should be rephrased as follows: "*As far as possible the lower end of the clinically effective dose range and the optimal dose should be determined in one or more dose-finding studies, usually with a randomized, controlled, parallel-group, fixed-dose design, evaluating at least 3 separate dose levels. It may be useful to include placebo and/or an active comparator in the dose-finding studies. In cases where the PK*	*effective dose range and the optimal dose should be determined in one or more dose-finding studies, usually with a randomized, controlled, parallel-group, fixed-dose design, evaluating at least 3 separate dose levels.* ***It is generally recommended to include placebo and/or an active comparator****. In cases where the PK the characteristics are similar across all age cohorts, dose response studies may be performed in a combined paediatric population (6-18 years).* ***Yet, it should be explored whether PK/PD is similar in the different age cohorts.****"* *Often, different efficacy is found with similar dosing between children and adolescents. In order to ensure optimal dosing, mere extrapolation from one age cohort to the other on basis of PK is not recommended.*

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		the characteristics are similar across all age cohorts, dose response studies may be performed in a combined paediatric population (6-18 years) or in one cohort and extrapolated to the other age cohort."	
Line 185-188		**Comments:** The statement "When taking methylphenidate as reference, the duration of trials can be short, i.e. 6 weeks on stable medication, the duration may be very dependent on the mode of action of the drug that is expected (fast or slow onset)" should be revised to remove reference to methylphenidate as an active comparator requiring a treatment duration of 6 weeks. The original dose-finding studies of products containing methylphenidate in children with ADHD were randomised crossover studies with each of the treatment periods lasting much less than 6 weeks (1-3 weeks). This is distinct from the treatment duration of 6 weeks in general in the confirmatory trials of methylphenidate products with a randomised, controlled, parallel-group design. **Proposed change (if any):** If this statement is incorporated in the guideline, it should be rephrased as follows: "***The treatment duration in dose-finding studies may vary depending on the expected mode of action of the investigational product (i.e. fast or slow onset) and the active comparator, if applicable. A treatment duration of 4 weeks on stable medication may be sufficient to inform the evaluation of dose response in subjects with ADHD".***	Partially accepted. An active comparator is still recommended. Therefore the text is amended accordingly: "***The treatment duration in dose-finding studies may vary depending on the expected mode of action of the investigational product (i.e. fast or slow onset) and the active comparator. A treatment duration of 4 weeks on stable medication may be sufficient to inform the evaluation of dose response in subjects with ADHD".***
190-194		**Comments:** Short-term trials – specifies parallel design studies only. Crossover designs may be suitable in this population if studies are of short duration and onset of action of medication rapid with rapid washout. Crossover designs have been accepted in registration trials for some stimulant medications.	Not accepted. Recommendations are made irrespective of type of medication. In order to improve consistency between trials a parallel design is considered first choice.

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Line 190		**Comments:** There is substantial overlap in trial design requirements in Section 6.1.3 with this section. More clarity is needed on dose finding study requirements vs. short-term efficacy studies requirements.	Text revision accepted under 6.1.3.
Line 193-194		**Comments:** The statement: *Separate studies are needed in children and adolescents* is somewhat contradictory to lines 106-107: *…children and adolescents should be separated or stratified*. See comment on line 106-107 and 177 above.	Text amended.
Line 195-200		**Comments:** Choice of control group – unnecessarily prescriptive as ethical considerations in using a placebo arm will change with the length of the study, use of an active comparator may result in many operational difficulties in studies and decreased generalizability of results (many subjects will have had prior treatment history with available agents that includes safety or tolerability issues and will not be eligible for enrolment, SEs from currently marketed agents easily identifiable and may lead to study unblinding) It is unclear in this section as to whether an Active control is needed in both pediatric age cohorts or in at least one of the age cohorts. The efficacy of ADHD treatments has been demonstrated in both child and adolescent populations. The percent reduction in symptoms and effect sizes in treatment trials for different treatments are similar in both the child and adolescent populations. Given this pattern of results, an active control in only one of the paediatric protocols would be acceptable, thus minimizing the need for exposure of an additional arm in an experimental protocol. We consider that the information obtained from either of the patient populations –children 6-11 years of age or adolescents 12-17 years of age – is sufficient to satisfy the requirement for comparative risk/benefit in the paediatric population. In addition an alternative study design evaluating the test compound with an active control in a child and adolescent population combined should be considered.	Partially accepted. In many trials, efficacy between children and adolescents is different, usually to be less in adolescents. Whether this is a matter of dosing or otherwise is not clear. Therefore, the guideline is rather strict on dose finding, but may indeed recommend to use the three arm design in the least sensitive population. The latter is to be decided by the investigator. The text has been amended under 6.2.1 to reflect these considerations.
Line 201-		**Comments:**	It is not clear what is expected here.

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205		No data reference provided to support this recommendation	
Line 202-203		**Comments:** See comment under Line 137-138 **Proposed change (if any):** Add after first sentence….In the case of methylphenidate, a washout period of **X** days should be applied.	Reference to methylphenidate is avoided.
Line 208-209		**Comments:** The statement "*Sample size should be calculated based on an effect size that is clinically relevant."* Should be revised for added clarity. **Proposed change (if any):** The revised statement should be: "*Sample Size should be calculated based on **a treatment effect** that is clinically relevant.*"	Accepted
Line 212-213		**Comments:** There is a highly significant genetic factor in ADHD. It is possible that biomarkers exist which may differentiate between the different subtypes. In such a case, it may be appropriate to investigate one subtype. **Proposed change (if any):** Suggested re-wording: If efficacy and safety are investigated in ADHD in general, analysis of effects on subtypes may be secondary.	No need to adjust the text. The guideline requires that treatment in ADHD combined type is demonstrated first. Until now, there are no valid data to accept efficacy in subgroups as primary objective. However, the guideline acknowledges ongoing research and developments in this respect (see under 2. SCOPE).
Line 213 - 214		**Comments:** The statement: *'Whether this may lead to specific claims depends on the acknowledgement of the subtypes as separate entities'* requires clarification. In particular whether there are there specific scientific criteria for acknowledging a sub-type as a separate entity, whether the use of DSMIV subtype criteria sufficient to justify such claims and whether this 'acknowledgement' will be known in advance or decided during the MA procedure?	The guideline is written in perspective of the update of DSM IV to DSM V (see under 2. SCOPE). Subtypes referred to are DSM defined subtypes. Yet, the guideline at present does not decide on accepting claims, which is left up to the decision of CHMP. The text is amended to reflect this view.
Line 214-215		**Comments:** The statement: "In the latter case the development of specific assessment scales for the different subtypes is needed." Should be revised. Development of specific scales may not always be needed as necessary information as the analysis of the effects on subtypes may be included in existing assessment scales **Proposed change (if any):** Revised statement should be: "*In the latter case the development of specific scales for different subtypes **may be** needed*"	Accepted
Line 217-		**Comments:** The statement: " This might be done by	Text partially amended. The open label character of a

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222		prolonging the time of double blind or by randomised withdrawal design" should be revised. Additionally the statement, "Patients are followed by at least 6 months for maintenance of effe**ct"** should be revised. These statements were refined to provide clarification to the paragraph in view of the 2 different study designs being proposed assuming that the 6 months duration would be required for the maintenance of efficacy period; i.e. Double Blind Placebo Controlled phase in a conventional randomised DB study and OL phase in a randomised withdrawal design study. **Proposed change (if any):** The revised statement should be: " This might be done by **a double-blind study up to six months** or by a randomized withdrawal design. The revised statement should be, " *Patients will be followed on* ***open label for at least*** *6 months to establish maintenance of effect*."	withdrawal design is not standard.
Line 228-229		**Comments:** The statement: "*Worsening or relapse has to be defined in the protocol and should be a clinical relevant increase of symptoms, scored on a validated rating scale at one or more visits*" should be revised. **Proposed change (if any):** The revised statement should be: " *Worsening or relapse has to be defined in the protocol and* ***could*** *be a clinical relevant increase of symptoms, scored on a validated rating scale at one or more visits* ***or the start of a therapy intended to treat the exacerbation of ADHD symptoms****."*	Not accepted. It is the opinion of CHMP that worsening of symptoms as assessed by a proper rating scale is the most reliable.
Line 235-239		**Comments:** Adults with ADHD are not a special population. Adult ADHD is a valid target for initial study of ADHD. In fact, in some cases, adult patients may be the preferred population to study novel compounds where it is desirable to reduce exposure in vulnerable paediatric patients and to minimize their exposure to the extent possible until efficacy / safety in adults have been established.	Text amended. However, for reasons of diagnostic and treatment validity, adult ADHD is not regarded a primary objective, yet to be part of a drug development program in children and adolescents. PK studies may be initiated in adults (see amended text under 6.1.2.
Line 238-239		**Comments:** The statement, "Hence, the special population is limited to adults (<65 years of age), and efficacy and safety should be demonstrated in this population separately" should be revised.	Elderly (> 65 years of age) are made part of the special populations. As is reflected in the guideline, separate efficacy/safety studies

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		The revised statement provides clarity that a separate maintenance of effect study will not be needed for the < 65 years age population. We would argue that a separate maintenance of effect study in this patient population would not be indicated if one had already been conducted in a paediatric population and the other way around. **Proposed change (if any):** The revised statement should be, "Efficacy and safety **in short-term trials** should be demonstrated in adults (<65 years of age) separately"	are needed in all different age cohorts. This includes maintenance of effect studies, withdrawal etc.
Line 240-244		**Comments:** The diagnosis and treatment of children under the age of 6 years is controversial, and requires specialized training and tools. Despite emerging research studies documenting the presence of ADHD in younger children, the appropriate identification of clinical cases remains challenging. The most recent European guideline for hyperkinetic disorder suggests the need for development and standardization of new tools for diagnosis, as well as adaptations of diagnostic criteria, in order to establish an accurate diagnosis. The recommended first-line therapy in this guideline for children less than 6 years of age is psychosocial intervention and parent training, with medication only considered after failure of response to first-line therapy and/or additional specialist assessment. There is still a lack of consensus in the field on the ability to diagnose ADHD in children less than 6 years of age, the limited availability of tools and diagnostic criteria, as well as a lack of consensus of the added value of pharmacotherapy over other interventions in this age group.	Acknowledged. Yet, because of the argumentation given, the guideline takes a pro-active position to allow future studies.
Line 247-248		**Comments:** The statement, "Mandatory for the diagnosis in adults is the verifiable presence of first symptoms in early childhood" should be revised. While confirmation that symptoms of ADHD were present before 7 years (as per current DSM –IV criteria) is necessary for the diagnosis of ADHD, documentation verifying that symptoms were present may not be readily available, especially for older adults who's records may not be accessible.	Text amended accordingly.

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		This statement as written might impact study enrolment and create a distribution of clinical subjects that are biased to the lower age range in adult studies. In cases where formal documentation or collateral corroboration was not available, we would argue that patient self-report in the context of a full diagnostic interview with a trained clinician is sufficient for diagnosis. **Proposed change (if any):** The revised statement should be, "***The presence of symptoms in childhood is a requirement for a diagnosis of ADHD in adults. As such, it is recommended that investigators attempt to obtain supporting documentation if available, independent of patient self report.***"	
Line 248-249		**Comments:** The statement, "*Borderline- and antisocial personality disorder are often found co-morbid*", is not aligned with the exclusion criteria found in section 4.2, Exclusion Criteria. We propose to revise the relevant exclusion criterion to allow enrolment of adult patients with ADHD with co morbid borderline- or antisocial personality disorder.	Text revised under 4.2.
Line 252		**Comments:** See comments above on studies in patients with and without co morbidities (line 108/109); these comments are also very relevant to this adult patient group given the higher frequency of co morbidity in the adult ADHD patient.	Restricted co morbidity is accepted for the confirmatory trials.
Line 256		**Comments:** The statement, "*A similar trial design as in children/adolescents can be used"*, may be interpreted to suggest that a separate maintenance of effect study should be conducted. We would argue that a separate maintenance of effect study in this patient population would not be indicated if efficacy in the treatment of ADHD symptoms was established in short-term trials in adults and maintenance of effect had already been demonstrated in the paediatric population. See comments to section 6.3, Studies in Special Populations, lines 238-239.	Short- and long term efficacy has to be demonstrated for each age cohort.
Line 258		**Comments:** "Significant other" is not a very clear term. **Proposed change (if any):** Replace by a more appropriate term for third-party assessment.	Significant other is common terminology in psychiatry, and refers to subjects who are close to the individual under investigation.
Line 264-		**Comments:** The statement: "*In small children, often, higher*	Accepted

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265		*doses are required*" should be revised. This is more likely to be the case with stimulants, and is an assumption for other medication, particularly with different mechanism of action. **Proposed change (if any):** The revised statement should be: *Different doses than those used in older children may be required in small children.*	
Line 267-268		**Comments:** The need for a prospective Cohort design for long-term safety follow-up as part of the RMP should be addressed in a case by case basis depending on important potential risks and on the amount of data on long-term exposure during the clinical development. **Proposed change (if any):** Change to "A prospective Cohort design for long-term safety follow-up may be needed as part of the Risk Management Plan to further evaluate important potential risks."	Long-term safety of psychotropic drugs has not been foreseen as of yet. With recent pharmacovigilance issues such as suicidal ideation/suicidality, and cardiotoxicicity, the guideline offers guidance to assess safety prospectively rather than in retrospect. Text not amended.
Line 280-281		**Comments:** The statement: "*Beyond the regular assessment of adverse events special attention should be paid towards the effects, short- and long-term, on the developing brain and bodily functions*" has questionable terminology. The terms, "developing brain" and "bodily functions", are vague and ill defined and should be deleted. **Proposed change (if any):** The revised statement should be: *"Beyond regular assessment of adverse events special attention should be paid towards the effects, short- and long term on the effects* ***of cognitive function and sexual maturation.****"*	Text amended as follows: "on the developing brain (e.g. adverse cognitive functioning) and bodily functions (see under 7.2.5).
Line 286-287		**Comments:** The statement: "For new candidate compounds, at least one short-term and one long-term trial should incorporate a short withdrawal period …" should be revised. As indicated in Section 6.2.2 of the draft guideline, randomised withdrawal will often be an integral part of the long-term efficacy study to establish maintenance of effect. This data may also inform the evaluation of rebound and withdrawal after long-term exposure. If there was no concern about either of these on the basis of randomised withdrawal after long-term treatment, then it would be reasonable to assume that this did not constitute a safety problem after shorter treatment	The argument for the need of only one trial where rebound/withdrawal is investigated is not accepted. Adaptation of receptors after long-term exposure to psychotropic drugs may be different compared to short-term exposure. Since treatment of ADHD may be, but is not necessarily, of long-term duration, rebound and withdrawal should be assessed in both situations. Text not amended.

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		durations. The safety of (abrupt) discontinuation could then be documented in an open-label or single-blind, placebo-controlled follow-up phase for a suitable length of time after the last dose of double-blind study drug in a short-term study. This data should be sufficient to indicate if rebound or withdrawal might be of concern after short-term treatment overall. **Proposed change (if any):** The revised statement should be: *"For new candidate compounds, at least one trial should incorporate a short withdrawal period. If rebound and withdrawal are not observed in a study with randomized withdrawal after long-term exposure, than there is no need to evaluate the potential for either of these occurring in a study with randomized withdrawal of shorter periods of exposure …"*	
Line 290-294		**Comments:** Standard pre-clinical dependence studies conducted in mature animals have historically identified molecules with abuse potential across all age groups. It is not clear as to why special studies would be required to identify dependence risk to the pediatric population. Could EMEA please provide the drivers that would suggest differential risk to the pediatric population and therefore the need for evaluation in pre-pubertal animals? Furthermore, could EMEA please provide clarity as to how this animal data will be used in human risk assessment? The current language in section 7.2.1 starting at line 290 implies that dependence studies in different aged animals will be expected. Currently there are no standard study designs for studies such as these utilizing animals that are "pre-pubertal". Endpoints in these types of studies are highly dependent on a number of variables, including endocrine status, environment and handling. Few laboratories have experience and/or expertise in conducting juvenile animals studies and even fewer, if any, have the expertise needed to conduct dependence studies in juvenile animals. Thus it will be difficult to interpret dependence studies in pre-pubertal animals and nearly impossible to predict human relevancy and risk. If these types of studies are expected, could EMEA please provide examples of designs for dependence studies in pre-pubertal animals?	The present guideline is the first to address a child psychiatric disorder, and consequently refers to the guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications (CHMP/SWP/169215/2005). This guideline promotes the development of the juvenile animal model to enhance safety assessment in children.

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Line 290-291		**Comments:** The statement: "Animal studies will be needed to investigate the possibility of dependence in new classes of compounds or when there is an indication that dependence may occur" should be revised/clarified. Medicinal products indicated for ADHD can be subdivided into CNS stimulants and non-stimulants. According to Section 5.2 of the CHMP Guideline on the Non-clinical Investigation of the Dependence Potential of Medicinal Products (EMEA/CHMP/SWP/94227/2004), the CNS stimulatory properties of an active substance can only be concluded after behavioural studies in animals have been performed or relevant observations in humans have been made. This Guideline further indicates that the dependence potential of CNS stimulants and medicinal products indicated for ADHD should be investigated using the drug self-administration animal model. **Proposed change (if any):** It should be clarified whether the statement applies to both CNS stimulants and non-stimulants, and whether an animal drug self-administration study suffices. The revised statement should include a cross-reference to the CHMP Guideline on the Non-clinical Investigation of the Dependence Potential of Medicinal Products (EMEA/CHMP/SWP/94227/2004).	Cross reference is made to the respective guideline.
Line 291-293		**Comments:** The statement, "*Differentiation between pre-and post pubertal status and adulthood is needed, because of ongoing brain development across the age span of 6-18 years, and the matured brain in adulthood.*" should be deleted from the guidance. There is very little experience with juvenile animal studies to investigate dependence potential. A regulatory request to conduct such studies is therefore considered premature and scientifically not justified. The scarce literature available focuses on animal models of peri adolescent substance abuse. Virtually no information is available on animal models addressing dependence potential in younger age ranges. It has been suggested that the effects of alcohol, nicotine or cocaine are different in periadolescent animals compared to	Text amended in accordance with the Safety Working Party.

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		adults. However, this concern does not apply to CNS stimulatory drugs like amphetamine. In fact, periadolescents animals treated with amphetamine tend to exhibit fewer effects associated with aversive reactions compared to adult ones (Smith, 2003: Animal models of periadolescent substance abuse; Neurotox. Teratol., 25: 291-301; Laviola et al., 1999: Psychobiological risk factors for vulnerability to psychostimulants in human adolescents and animal models, Neurosci. Biobeh. Rev., 23: 993-1010). Accordingly, the addictive risk of psychostimulants is considered less in periadolescent animals than in adults. In the absence of a concern for CNS stimulants, there is not a concern for non-stimulants either. Besides the above considerations, numerous technical issues on the conduct of juvenile animal studies on dependence potential are to be solved. These issues include the selection of animal species, age range of the test animals (prepubertal and/or pubertal), duration of training procedures, and selection of test parameters and positive controls. For instance, rats are in the juvenile/prepubertal age range approximately between postnatal Day 22-35 (i.e. roughly during 2 weeks). It is unclear how juvenile rats can be appropriately trained, and subsequently the actual test procedures be conducted, within such a short period of time. Another example is the technical difficulty of maintaining indwelling intravenous catheters in small-sized juvenile animals to be tested in intravenous self-administration studies on abuse potential. Furthermore, clarification is needed on the difference between the “postpubertal” age and adulthood. If this statement is incorporated in the guideline, it should be revised/clarified: – does this statement apply to both CNS stimulants and non-stimulants? – what should be the design of a juvenile abuse liability study in terms of animal species, age range of the test animals (prepubertal and/or pubertal), duration of training procedures, and selection of test parameters and positive	

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		control? – what is the difference between "postpubertal" age and adulthood? **Proposed change (if any):** The statement, "*Differentiation between pre-and post pubertal status and adulthood is needed, because off ongoing brain development across the age span of 6-18 years, and the matured brain in adulthood.*" should be deleted from the guidance.	
Line 293-294		**Comments:** The statement, "Based on the results of the animal studies, in vivo studies in humans may be required." should be revised since conducting studies in children or adolescents for the sole purpose of assessing abuse liability without the prospect of therapeutic benefit will raise ethical concerns. Traditionally, abuse liability studies involving the administration of a single, supratherapeutic dose of the test product and an active control will be conducted in adult subjects with a history of recreational drug use or current diagnosis of substance use disorder, who are otherwise healthy. Even if this type of subject could be identified in the paediatric population, it would be very difficult to justify conducting interventional studies without therapeutic benefit in these subjects. **Proposed change (if any):** The revised statement should be, *"Based on the results of the animal studies, in vivo studies in **adult** humans may be required."*	Accepted. Text amended with the text: **(preferably in healthy adult subjects)**. Text slightly modified from proposal.
Line 299-300		**Comments:** We question the appropriateness of adding "mood" in the following statement, "Similarly it may be necessary to monitor psychiatric side effects (e.g. depression, mania and mood)", As both depression and mania are already specified, the more general term, "mood", seems redundant. **Proposed change (if any):** The revised statement should read: "*Similarly it may be necessary to monitor psychiatric side effects (e.g. depression, mania)"*.	Not accepted. Mood changed may be different from actual depression or mania.
Line 301-303		**Comments:** The location of this section under clinical safety evaluation seems to suggest that specific measurements are required in all trials and not only the early trials with very frequent visits which allow monitoring indeed to be	Accepted

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		'continuous'. We would like to ensure that sponsors can choose any instrument they wish if scientifically justified. The statement, "*Special attention should be paid to attempted and completed suicides*", seems to indicate that this assessment can be based on prospective data collection using a relevant scale such as the C-SSRS or the review of aggregate safety data after completion of a cohort or complete study. Published data suggest that this assessment can be reliably made for patients with ADHD on the basis of a blinded review of patient narratives for cases identified using an electronic text string search of adverse event data and categorization using the C-CASA classification (Bangs ME, Tauscher-Wisniewski S, Polzer J, et al. Meta-analysis of suicide-related behavior events in patients treated with atomoxetine. *Journal of the American Academy of Child & Adolescent Psychiatry* 2008; 47(2): 209-18). Regarding "*The Columbia Suicide Severity Rating Scale by Posner et al16 is currently used in many studies, but alternative scales may be used as well*." In order to ensure comparability, the recommendation to use the CSSRS should be strengthened, or more direction given on elements that should be present in alternative scales to allow comparison with outcomes from the CSSRS. The reference cited (16) describes the classification method C-CASA and NOT the C-SSR which is a prospective standardised documentation method for suicidal ideation and behaviour which maps to the categories of C-CASA. The validity, sensitivity, specificity, and meaningful analysis of the Columbia Suicide Severity Rating Scale in this population have not been established. **Proposed change (if any):** The revised statement should read, *"Special attention should be paid to attempted and completed suicides by using a suitable suicide rating scale or review of relevant AE data. Suicidality should be prospectively assessed to map into the categories defined by the C-CASA method (ref 16) . Although not validated for children and adolescents, C-SSRS is an existing documentation system that allows documenting according to the C-CASA categories but alternative approaches may be used as well.*	

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Line 308-310		**Comments:** The statement, "*Special attention should be paid to cardiotoxicity, i.e. hypertension, arrhythmias conduction disorders, in particular QT interval prolongation, if medicinal product belongs to a class associated with cardiovascular effects.*" should be revised since QT interval prolongation is not the result of a cardiac conduction disorder but a repolarization disorder. **Proposed change (if any):** The revised statement should read, " *Special attention should be paid cardiotoxicity, i.e. hypertension, arrhythmias, conduction disorders, **repolarization disorders**, in particular QT interval prolongation, if medicinal product belongs to a class associated with cardiovascular effects.*"	Accepted
Line 316-317		**Comments:** The statement, "*Depending on the pharmacological properties of the new therapeutic agent, the investigation of endocrinological parameters may be necessary (prolatine secretion, adrenal homones etc.)*" should be revised to correct a typographical error. In addition, HPA axis hormones are more appropriate to investigate than adrenal hormones without the determination of corresponding pituitary hormones. **Proposed change (if any):** The revised statement should read, "*Depending on the pharmacological properties of the new therapeutic agent, the investigation of endocrinological parameters may be necessary (**prolactin** secretion, **HPA axis** hormones etc.)*"	Accepted
Line 321		**Comments:** For consistency with lines 325-326, the sentence: "Long-term safety trials are mandatory in ADHD as childhood onset disorder." is proposed to be slightly revised. **Proposed change (if any):** Change to "Long-term safety data are required in ADHD as childhood onset disorder and can be generated by open label extension of short-term studies and/or by specific long-term trials".	Text amended accordingly in the text where appropriate.
Line 321-323		**Comments:** The statement, "*Special attention should be drawn towards the effects of the developing brain and body, and the susceptibility to the "known" side effects of psychotropic drugs in children, that may be altered or enhanced*" should be clarified since the terminology of "developing brain" is ambiguous. See previous comment in	Text amended according to previous changes made.

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		section 7.1, General Recommendation, line 280-281.	
Line 327-328		**Comments:** The need for a prospective long-term safety follow-up as part of the RMP should be addressed in a case by case basis depending on important potential risks and on the amount of data on long-term exposure during the clinical development. **Proposed change (if any):** Delete "…and prospective follow-up for a longer period of time should be part of the Risk Management Plan (RMP) post-licensing. A prospective cohort design is recommended (see safety section)".	Not accepted. The guideline is instigated to enhance the assessment of safety data in children and in particular long-term safety data for psychotropic drugs. So far, no systematic long-term safety data have been assessed in either study. This may be the reason for recurrent safety issues identified within the pharmacovigilance domain. Therefore, the current recommendation will be maintained.
Line 330-331		**Comments:** The statement, "*The assessment of dependence and abuse potential after prolonged exposure is mandatory, and interaction with other psychotropic drugs needs to be investigated.*" should be revised. Unless there is a concern on the basis of appropriately designed short-term studies (e.g. abuse liability and drug-drug interaction studies in healthy subjects), there should be no need to evaluate the abuse potential or drug interactions in specifically designed long-term studies in the target population. Long-term efficacy and/or safety studies that would otherwise be conducted in the adult population should be sufficient to inform the evaluation of abuse potential after prolonged exposure (e.g. treatment compliance), and the interaction with other psychotropic drugs (e.g. AEs and population PK analysis). **Proposed change (if any):** The revised statement should read, "***Long-term studies in adults may inform the evaluation of dependence and abuse potential after prolonged exposure, and the interaction with other psychotropic drugs****".*	Text revised in: The assessment of rebound and withdrawal.
Line 332-333		**Comments:** The need for a prospective long-term safety follow-up as part of the RMP should be addressed in a case by case basis depending on important potential risks and on the amount of data on long-term exposure during the clinical development. **Proposed change (if any):** Change to "Long-term safety assessment for the different age cohorts may be needed as part of the RMP. A prospective cohort design would be recommended in this case".	Not accepted, see earlier comment (Line 327-328).
6.2.2	**6**	**Comments:** We support the need for demonstration of long-	It is up to the investigator to use either a longer period of

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		term value, but have grave reservations about the requirement for a placebo arm in a long-term trial. A requirement for such a withholding of treatment over a long term would encounter major ethical difficulties (as well as substantial problems of feasibility). Other methods (randomised comparison with active comparator or with treatment-as-usual; propensity analysis; placebo-controlled discontinuation) should be available and avoid harm to subjects. We think the requirements for withdrawal studies to assess long-term efficacy should be specified and clarified, as follows: "Patients should be followed for at least 6 months to study maintenance of effect in open-label condition. If a placebo-controlled withdrawal period is undertaken thereafter it should last for long enough to assess relapse and in any case for at least 6 weeks. Dose reduction in a discontinuation trial should be gradual to avoid acute withdrawal/ rebound effects".	double blind or to use a withdrawal design. Both are mentioned in the text.
6.3.1		**Comments:** We support the general proposals for trial in adults. However, the requirement, for the diagnosis in adults, that there should be a "verifiable presence of first symptoms in early childhood" should be reconsidered: (i) 'verifiability' is seldom achievable and is not required by the DSM-IV definition; (ii) current scientific evidence suggests no significant differences in efficacy of ADHD medication according to age of onset; (iii) age of onset is an unreliable measure and "early" could be interpreted in different ways; (iv) it seems likely that the revision of diagnostic schemes (DSM-V) will modify or even abandon an early-childhood-onset requirement. We would suggest phraseology such as "presence of first symptoms in childhood" (ie omitting "verifiable" and avoiding "early"). This would be a better match with the DSM and ICD definitions. We also support the general considerations for pre-school children and the need for a long-term safety follow-up. However, the phase that "often higher doses are required" for this population is open to misinterpretation; we are not aware of empirical evidence to this effect and would prefer the phrase to be omitted.	Text amended according to earlier comments made.
7.1		**Comments:** Development of a standard method for adverse event recording for ADHD medications is recommended, and	It is not understood what is meant here, other than the general way of collecting adverse events at regular times.

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		should be tailored to the age group under investigation.	
126	**7**	**Comments:** We believe it is important to add that the child/adolescent consent should be obtained. In the event of a long term study, this consent should be reassessed on a regular basis, i.e. every six months **Proposed change (if any):** At the end of line 126 add this recommendation	The guideline should be read in conjunction with the ICH E11 where ethical issues are discussed.
164		**Comments:** We believe it is important to add the importance to collect patients' feelings using a patient diary card. Many times patients do not report the ability/inability to perform daily activities, which may have a significant impact on their QoL. **Proposed change (if any):** At the end of line 164 add a paragraph with the recommendation to collect daily information with a patient's diary card.	Text amended with: 'A patient diary card may also be suitable in this respect'.
232		**Comments:** We believe it is important to include the opportunity to use adaptative design. Considering the rarity of patients, sponsors should be encouraged to use this design in a multiple dose Phase II design, moving then into a Phase III with the best selected dose. **Proposed change (if any):** At the end of line 195 add a paragraph stimulating the use of adaptative designs, especially suggesting to combine Phase II and III.	There is no need for adaptive design because of rarity of patients. ADHD has a 5-6% prevalence rate. Because of allowing co morbidity in confirmatory trials, but not dose finding/proof of concept trials, an adaptive design is not considered suitable. No text amendment.

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Line 129-130 1st bullet	**8**	**Comments:** The exclusion criterion, "another Axis I disorder (co-morbidity) with the exception of ODD/CD (as mentioned for confirmatory trials), albeit that ADHD should be the primary diagnosis" should be revised. Subjects with a lifetime diagnosis of relevant comorbid Axis I psychiatric disorders, which are currently asymptomatic and clinically stable for the comorbid condition should not be excluded. Given how common these co-morbidities are with ADHD, this exclusion could limit enrolment and decrease the ability to generalize the findings to a broader patient population. **Proposed change (if any):** If this statement is incorporated in the guideline, it should be re-phrased as follows: "***Current diagnosis of*** *another Axis I disorder (co-morbidity) with the exception of ODD/CD (as mentioned for confirmatory trials), albeit that ADHD should be the primary diagnosis*"	Text amended.
Line 180		**Comments:** Typographical error **Proposed change (if any):** "bet" should be change to "be"	Corrected
301- 302		**Comments:** The statement, "*Special attention should be paid to attempted and completed suicides*", to indicate that this assessment can be based on prospective data collection using a relevant scale such as the C-SSRS or the review of aggregate safety data after completion of a cohort or complete study. Published data suggest that this assessment can be reliably made for patients with ADHD on the basis of a blinded review of patient narratives for cases identified using an electronic text string search of adverse event data and categorization using the C-CASA classification (Bangs ME, Tauscher-Wisniewski S, Polzer J, et al. Meta-analysis of suicide-related behavior events in patients treated with atomoxetine. *Journal of the American Academy of Child & Adolescent Psychiatry* 2008; 47(2): 209-18). **Proposed change (if any):** The revised statement should read, *"Special attention should be paid to attempted and completed suicides* ***by using a suitable suicide rating scale or review of relevant AE data".***	Text amended according to other comments made.
Line 330-331		**Comments:** The statement, "*The assessment of dependence and abuse potential after prolonged exposure is mandatory, and interaction with other psychotropic drugs needs to be investigated.*" should be revised. Unless there is a concern on	Text amended.

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		the basis of appropriately designed short-term studies (e.g. abuse liability and drug-drug interaction studies in healthy subjects), there should be no need to evaluate the abuse potential or drug interactions in specifically designed long-term studies in the target population. Long-term efficacy and/or safety studies that would otherwise be conducted in the adult population should be sufficient to inform the evaluation of abuse potential after prolonged exposure (e.g. treatment compliance), and the interaction with other psychotropic drugs (e.g. AEs and population PK analysis). **Proposed change (if any):** The revised statement should read, "***Long-term studies in adults may inform the evaluation of dependence and abuse potential after prolonged exposure, and the interaction with other psychotropic drugs***".	
Section 1	**9**	**Comments:** Regarding ADHD DSM-IV TR Diagnosis versus HyperKinetic Disorder ICD-10 diagnosis: The possibility of a common development plan integrating both EU and US approach is important, as it would be difficult to develop a drug specifically for EU.	The guideline takes an EU position. However, both DSM and ICD are acceptable.
Section 4		**Comments:** Regarding comorbidity: Some comorbidities offering unique challenges like Bipolar disorders, and therefore a common position between the EMEA and the FDA would be helpful. **Proposed change (if any):** As comorbidity is the rule in child and adolescent psychiatry, acceptable comorbidity should be specified.	Acceptable co morbidity has been specified.
Section 6		**Comments:** Regarding type of studies and potential extrapolation: Is there any potential extrapolation from one age group to another either in terms of Safety or Efficacy (short-term or long-term)? **Proposed change (if any):** Please clarify possibilities for such extrapolation, if any.	Efficacy/safety, both short- and long-term are required for each age cohort. The text has been amended to allow larger trials in larger age cohorts (children and adolescents together). Because of the possible shift in symptom presentation, no extrapolation for efficacy is deemed appropriate. For the safety part, the developmental state and subsequently brain maturation, requires safety assessment not to be extrapolated.
Section 6.1		**Comments:** Is there any potential based on linear PK for a sponsor to be able to further have the ability to extrapolate data? **Proposed change (if any):** Please clarify such an approach	The connotation that 'sparse sampling and modelling techniques should be applied where possible' already reflects the possibility to extrapolate data if justified.

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		can be used, if at all.	
Section 6.2		**Comments:** The statement in lines 193-194: *Separate studies are needed in children and adolescents* is somewhat contradictory to lines 106-107: *…children and adolescents should be separated or stratified*. **Proposed change (if any):** Please specify type of studies for each age group. Please clarify the possibility of having only one study, including both children and adolescents, rather than two studies.	Text amended.
	10	**n.a.**	
Line 8	**11**	**Comments:** Clinical development programs should also take into account adult ADHD **Proposed change (if any):** Add: …….evaluation of new medicinal products in ADHD with focus on the childhood onset **and long term management in adults.**	Not accepted. It is felt by CHMP that the childhood onset of ADHD is the main focus of the guideline.
Line 31-45		**Comments:** Adult ADHD presents itself differently from child ADHD **Proposed change (if any):** A description of adult ADHD and diagnosis should be provided	Not accepted. The change in symptoms from childhood into adulthood is mentioned.
Line 33		**Comments:** DSM IV criteria focus on child ADHD and are not very suitable for diagnosis in adults. How reliable is the retrospective assessment of the symptom descriptions and diagnostic criteria for adults that refer to the situation before the 7th year of life? We believe that in the diagnosis of adult ADHD, the experts are more likely to go back no further than the 12th year of life, when retrospectively questioning adults. See also comment in Line 248 **Proposed change (if any):** A recommendation for a suitable diagnostic tool for adult ADHD should be provided.	The guideline relies on DSM for all age cohorts. There are no other instruments/tools available for Adult ADHD.
Line 39		**Comments:** Provide more details on ADHD subtypes and also consider adulthood. See also comment in Line 60 – 63. **Proposed change (if any):** The relative prevalence for each subtype should be provided. For example, the combined type is more commonly seen in health centres, whereas ADHD-HI is hardly seen. Children with ADHD-IA are much harder to find, since the associated symptoms lead less quickly to behavioural problems and therefore less referrals to health centres. While hyperactivity is common in children with ADHD, it tends to	There are no data available to get into more detail regarding subtypes.

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		disappear in adulthood. In contrast, half of the ADHD children continue to have attention difficulties in adulthood.	
Line 40		**Comments:** ICD-10 classification is mentioned here, but no where else in the guideline. **Proposed change (if any):** Greater explanation should be provided on when and how to use ICD-10, especially because the ICD-10 criteria differ significantly in terms of severity to the DSM-IV criteria.	There is no guidance in how to use DSM or ICD. It is up to the investigator to choose either one, but preferences will learn that within the EU, DSM classification is first of choice.
Line 51		**Comments:** It states, ADHD should be discriminated from oppositional behaviour due to repeated failure in performance and the incapability of living up to expectations. We question whether such criteria adequately discriminate ADHD from Oppositional Defiant Disorder or Conduct Disorder.	Text amended to follow the differential diagnoses as in the DSM.
Line 60 - 63		**Comments:** Propose to break down by subtypes and provide the relative prevalence for each subtype. ~~See also comment in Line 39.~~	No reliable data available. See also comment in Line 39.
Line 63 - 64		**Comments:** The Finish study might not have been representative. We think that the combined type is the most prevalent group.	Reference has been deleted.
Line 71		**Proposed change (if any):** Add:…. In older adolescents, the ratio of male-to-female ADHD is approximately 1:1, while among young adults ADHD is about 2-fold more predominant in women (Dulcan M (1997) *J Am Acad Child Adolesc Psychiatry* **36 (**10 Suppl) 85S–121S).	Not accepted. Data are insufficient to amend the text accordingly.
Line 76		**Comments:** Co-morbidities need to be taken into consideration when conducting clinical trials. **Proposed change (if any):** Add:… In adult ADHD, co-morbidities can include depression, anxiety, bipolar disorder, learning difficulties and substance abuse.	Accepted co morbidities for trials in adult ADHD are mentioned.
Line 107		**Comments:** Should not neglect adult ADHD. **Proposed change (if any):** Add: …separate studies in adults (> 18 years) should be conducted.	Text amended. The adult section has been integrated.
Line 108-109		**Comments:** ADHD patients without co-morbidities are difficult to find **Proposed change (if any):** Reword sentence to: For primary dose-finding studies, inclusion patients with ADHD without significant co-morbidities is recommended. Given the rarity of	Not accepted. For reasons of treatment validity, the guideline recommends to be as strict as possible in the phase II studies and take an easier position in the phase III studies.

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		pure ADHD patients, however, ADHD patients with certain co-morbidity could be acceptable, provided that confounding factors are taken into consideration. Otherwise interpretation of study results……	
Line 119-120		**Proposed change (if any):** Add reference to relevant guidelines for proper scales	Cross reference has been made to the Depression and Anxiety Guidelines.
Line 144		**Comments:** Is the Conner's rating scale valid for all ages (in terms of validity / reliability)?	The Conner's rating scale is one of the most common scales used in ADHD over the past decade. The scale is mentioned because of its use in common practice, but alternatives are given as well. According to literature, as an instrument is has never been validated properly.
Line 180		**Comments:** Typo **Proposed change (if any):** Special interest should **be** taken…	Corrected
Line 241		**Proposed change (if any):** Add reference to adjusted assessment tools.	A general reference to available assessment tools is provided
Line 246		**Comments:** The diagnosis of ADHD in adults should **NOT** be similar to that of children. DSM IV is inadequate as a tool. Questioning the patient, parents and teachers about events in childhood would be highly unreliable. **Proposed change (if any):** A recommendation to develop appropriate diagnostic tools for adult ADHD should be given.	Not accepted. Without other instruments/tools, the guideline relies on DSM or ICD classification.
Line 248		**Comments:** How is early childhood defined? See also comment in Line 33.	Text has been amended (early) childhood. Referred is to children under the age of 18.
Line 252-253		**Comments:** Same comment as under Line 108-109.	See comments on lines 108-109.
Line 301		**Comments:** It states, suicidal ideation and behaviour should be monitored carefully. But in which studies? **Proposed change (if any):** Specify in which studies, .e.g. patient studies (dose-finding and confirmatory) and not healthy volunteer studies.	Suicidal ideation etc should be monitored in all therapeutic trials in all age cohorts.
Line 327		**Comments:** Typo **Proposed change (if any):** …should be **part** of the Risk	Corrected

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		Management Plan…	