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

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON CLINICAL EVALUATION OF MEDICINAL PRODUCTS USED IN WEIGHT CONTROL

ADDENDUM ON WEIGHT CONTROL IN CHILDREN

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	MERCK SHARP & DOHME (EUROPE) INC	
2	ROCHE	
3	ASSOCIATION OF THE EUROPEAN SELF-MEDICATION INDUSTRY (AESGP)	
4	EFPIA	

Table 2: Discussion of comments

COMMENTS FROM MERCK SHARP & DOHME (EUROPE) INC (MSD).		
GENERAL COMMENTS		
MSD applauds the CHMP for its proactive stance on obesity as a serious and life-threatening disease which requires long-term therapy to induce and maintain weight loss and the importance of pharmacotherapy as an adjunct to dietary measures and physical exercise. Obesity is a significant worldwide health problem. It is associated with an increased risk of Type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, gallstones, osteoarthritis, certain forms of cancer, and an overall reduced life expectancy. It is apparent, therefore, that, beyond the intrinsic value in achieving weight loss, improvement in co-morbid conditions is clearly important. MSD agrees with the CHMP that childhood obesity warrants attention and welcomes this addendum on weight control in children.		
SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Page 3, Lines 28 - 36	"*However, in children the situation is more complex as the BMI changes substantially with age. BMI SDS (Standard Deviation score of patient's body mass index) is used to define childhood overweight and obesity in this guideline. The BMI SDS is based on pooled international data that links the accepted adult cut-off points, a BMI of 25 Kg/m2 for overweight and 30 Kg/m2 for obesity, to body mass index centiles for children while constructing bridging cut-off points related to age for children (Cole TJ et al. Eur J Clin Nutr 2005; 59:419-425).*" While MSD agrees that international data should form the basis for defining overweight and obesity in children, we suggest that BMI cut-off points (and not BMI SDS) as detailed in Table 4 in a paper by Cole TJ et al. BMJ. 2000; 320: 1-6 be used instead.	MSD suggests that these sentences be replaced with: However, in children the situation is more complex as the BMI changes substantially with age. BMI cut-offs based on pooled international data that link the accepted adult cut-off points (a BMI of 25 Kg/m^2 for overweight and 30 Kg/m^2 for obesity) to cut-off points related to age and sex for children (Table 4 in Cole TJ et al. BMJ. 2000;320:1-6) should be used to define overweight and obesity in the paediatric population. Comment: Agree. Rationale: the cut-off points related to age and sex for children serve as a standard definition for child overweight and obesity linked to the adult cut-off points of a BMI of 25 and 30 kg/m^2. The development of these is described in Cole TJ et al. BMJ. 2000; 320:1-6. In response to the comment, confirmation was sought in May 2008 from the Experts that attended the Ad Hoc Experts Group Meeting on Obesity in Children held London, 25th October 2006 (Doc Ref EMEA/497809/2006) that the cut-off points derived by Cole in 2000 remain the reference dataset for this guidance document. The Experts confirmed this was the case and the text was amended in line with the

		comment received.
Page 4, 49 - 56	"*In this guideline the following two categories are used to define subgroups of the paediatric population: 1. Younger Children, and 2. Adolescents, categorized as follows:* 1. *Younger children: ages from 6 to 10 years (or puberty) for girls and 6 to 12 years (or puberty) for boys* 2. *Adolescents: age from 10 years (or puberty) to 18 years for girls and from 12 years (or puberty) to 18 years for boys."* This classification using both age and pubertal development to define one of the bounds is difficult to interpret, and confusing. It is not clear if the group classified as Younger Children (6-10 years or puberty for girls, and 6-12 years or puberty for boys) will have both prepubertal and early pubertal girls (6-10 years old) and boys (6-12 years old). Similarly, it is unclear if the Adolescent group will have prepubertal girls (10 and older) and boys (12 and older) in addition to those that are in puberty. MSD suggests use of one categorization to avoid this confusion	MSD suggests that these sentences be replaced with: In this guideline the following two categories are used to define subgroups of the paediatric population: 1. Younger Children, and 2. Adolescents, categorized as follows: 1. Younger children: age 6 years old to onset of puberty 2. Adolescents: onset of puberty to age 17 years. Onset of Puberty: Girls/females: Tanner II breast development. Boys/males: Testicular Volume 4 mL (Tanner II) Comment: Disagree with the proposed wording but agree with underlying rationale. Therefore the following two categories are used to define subgroups of the paediatric population in the guideline, pre-pubertal and post-pubertal, categorised as follows: 1. Pre-pubertal: age 6 years old to onset of puberty as defined by a Tanner stage of 2. 2. Post-pubertal: post-puberty to age 18 years Due to the proposed length of the required studies and the difficulty in controlling for confounding, it was decided that pubertal children, in particular those in Tanner Stages 3 and 4, need not be included in the studies to determine efficacy. It is recognised in the guideline that some pre-pubertal children may enter puberty during the clinical trial.
Line 110	"*In the case of co-morbidities or parental obesity the BMI SDS threshold for study inclusion could be lowered.*" This guideline is not clear as it stands. And consistent with the suggested changes to lines 28-36 detailed above, BMI cut-offs would be appropriate.	MSD suggests that this sentence be replaced with: Overweight patients with obesity-related co-morbidities or parental obesity could be included in the study. Comment: Agree with proposed wording but, on further consideration, parental obesity was dismissed as an additional reason to put children on pharmacological treatment. Instead it was considered that if the parents were also obese, a family therapy was needed because otherwise the child would maintain the bad eating habits/lifestyle of the family. Therefore, the final wording is:

		'Overweight patients with obesity-related co-morbidities could be included in the study.'
Line 150-152	"*It is recommended that the primary endpoint is a change in BMI SDS*[2] *as described in the definition of obesity in children above. In adults a 10% weight reduction is accepted as a positive endpoint. However the degree of change should be justified by the applicant.*" Better definition of the parameter(s) to be followed and meaningful response to therapy is sought. MSD suggests that the EMEA guidelines specify the use of BMI to follow changes in adiposity over time in obese paediatric patients (Cole TJ et al. Eur J Clin Nutr. 2005;59:419-425) and that a placebo subtracted change of 5% in BMI from baseline over 1 year would be a meaningful response in this population. An alternative criterion should also be provided—the proportions of patients who lose at least 10% of their BMI at the end of 1 year.	MSD suggests that these sentences be replaced with: It is recommended that the primary endpoint be a percent change in BMI from baseline. A placebo subtracted change in BMI of 5% from baseline would be considered a meaningful response at the end of 1 year of intervention. Proportions of responders in the various treatment groups could be considered as an alternative primary efficacy criterion where response is at least 10% loss of BMI at the end of a 1-year period. Comment: In response to comments received regard the primary endpoint, the following additional question was posed to the Experts that attended the Ad-Hoc Meeting in 2006 i.e. *Should change in BMI SDS be replaced by change in BMI or BMI % as the primary efficacy endpoint re. change data*? Based on their responses and following further discussion at the EWP the following was agreed as the primary efficacy endpoint: *'It is recommended that the primary endpoint is a change in BMI Standard Deviation Score; however, change in adiposity should also be measured in BMI (%) units*[4]*. In adults a 10% weight reduction is accepted as a clinically meaningful effect. However, in the paediatric population the degree of change should be justified by the applicant'.*

COMMENTS FROM ROCHE
GENERAL COMMENTS
SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Addendum for weight control in children, section 2	While the main guideline differentiates BMI values between Asian/Pacific Island Populations and the other populations, the addendum does not. How are the BMI values calculated in these paediatric populations?	Comment: Cole et al obtained data on body mass index for children from six large nationally representative cross sectional surveys on growth from Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the United States. It probably reflects Western populations adequately but lacks representation from other parts of the world. The Hong Kong sample may, however, be fairly representative of the Chinese, and the Brazilian and US datasets include many subjects of African descent. Although additional datasets from Africa and Asia would be helpful, stringent inclusion criteria of a large sample, national representation, minimum age range 6-18 years, and data quality control, mean that further datasets are unlikely to emerge from these continents in the foreseeable future. It is not realistic to wait for them because there is an urgent need for international cut off points now. Also, Cole et al's methodology aims to adjust for differences in overweight between countries, so it could be argued that adding other countries to the reference set would make little difference to the cut off points. None the less, further research is needed to explore patterns of body mass index in children in Africa and Asia. However, the Cole data is considered as sufficiently internationally representative.

COMMENTS FROM THE ASSOCIATION OF THE EUROPEAN SELF-MEDICATION INDUSTRY (AESGP)
GENERAL COMMENTS
SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
11	Not only eating patterns and extent of physical activity have been associated with the increasing prevalence of obesity, e.g. shorter sleep.	At a minimum, “other factors” in the development of obesity should be mentioned. Comment: Disagree. Rationale: unclear re. ‘other factors’
71 and 120	A run-in period of 3-6 months is not feasible, because adherence to the trial protocol would likely be very low, resulting in very high dropout rates.	(1) Lack of efficacy of non-pharmacologic approaches tried in the past by patients in the study should be documented (2) The run-in period should be limited to 4 weeks Comment: Disagree. Rationale: the run-in period (without any medication) should last 3 to 6 months. All the non-medicinal interventions (lifestyle changes, diet, exercises frequency, parental involvement) should be recorded from the start of this run-in phase, continue during the blind treatment phase and persist later during the follow up phase. As agreed re. Adult Guidelines a run in period is needed to identify well motivated subjects and understand the nature of their conditions and to ensure that subjects are able to comply with lifestyle modification. The role of a run in period is to establish a pattern and to standardise as much as possible lifestyle intervention and motivation factors for patients.
134-136	To obtain 1-year data from patients who dropped out of the trial will only rarely be possible. In addition, there is no reason to expect that the well known rebound effect after termination of medicinal treatment will not be apparent in children.	The request to obtain 1-year data in patients who dropped out of the study should be deleted. Comment: Disagree. Rationale: ITT analysis is the preferred methodology in line with adult guidance document.
138-139	To observe patients for “6 months at least” after the end of the drug therapy will be very difficult and the percentage of patients that will be lost to follow-up is expected to be high. In addition, it is not clear how such a long follow-up period would further the assessment of efficacy and safety in this patient population.	The follow-up period should be shortened to 4-6 weeks. Comment: Disagree. Rationale: Effect of treatment encompasses both weight loss and maintenance. As agreed by the Ad-hoc Experts, after discontinuation of treatment the patients should be followed to assess relapse and/or rebound. This could be done formally after re-randomisation, but observation might also be a possibility, depending of what was known of the product and its class. The observation phase after

		drug therapy cessation should continue for at least 6 months. The possibility of too strong effect of the drug (excessive weight loss) is considered unlikely and related to dose problems rather than the duration of the study. In case the companies would like to conduct studies of shorter treatment durations, they should seek Scientific Advice. Problems related to compliance in adolescent's population should be foreseen in the design of the study.

COMMENTS FROM EFPIA

GENERAL COMMENTS

EFPIA welcomes this important addendum to the adult guideline but would like to emphasise the importance of global consistency (in particular with the guidance documents pertaining to the same patient population which are released by other regulatory agencies).

This Addendum specifically deals with paediatric drug development, as it will be discussed with the Paediatric Committee (PDCO) when submitting a Paediatric Investigation Plan (PIP). Therefore, we **would like to be reassured that this Addendum has been discussed with and endorsed by the PDCO**. It is of the greatest importance that our concerns regarding age classification (differing from ICH E11 standard) are addressed and that proposals for waivers for specific age classes (should it be considered as automatic "age class waivers" with no need to request specific individual product waivers?) be endorsed by the PDCO.

Comment: This Guideline was reviewed by the PDCO but as it is a CHMP Guideline, it does not receive formal endorsement by another Committee.

1. INTRODUCTION (BACKGROUND)

Line no. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
11	Not only eating patterns and extent of physical activity have been associated with the increasing prevalence of obesity, e.g. shorter sleep.	At a minimum, "other factors" in the development of obesity should be mentioned. Comment: previously addressed re. MSD comments

2. DEFINITION OF OBESITY IN CHILDREN

Line no. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
Section 2 Lines 23-26	International Diabetes Federation has recently published a consensus report on the Metabolic Syndrome and in this consensus childhood/adolescence abdominal obesity is defined as waist circumference of the 90th percentile or more (Paediatric	International Diabetes Federation (IDF) has recently published a consensus report on the Metabolic Syndrome (Paediatric Diabetes 2007: 8; 299-306). Childhood and adolescence abdominal obesity is defined as waist circumference of the 90th percentile or more Use of 90th percentile for children and the adult IDF metabolic syndrome criteria for waist

	Diabetes 2007: 8; 299-306).	circumference for adolescence 16 year or older makes it possible to define obesity globally as well as to compare studies between nations. Comment: Disagree. As previously stated, in response to external comments, confirmation was sought from the Experts that attended the 2006 ad-hoc meeting that the cut-off points derived by Cole in 2000 remain the reference dataset for this guidance document. The Experts confirmed this was the case and the text was amended in line with the comment received. See above re. Cole TJ et al. BMJ. 2000; 320:1-6.
Lines 28-32	The document states that the **BMI SDS should be used to define childhood obesity.** However, reference #2 (Cole *et al.*, *European Journal of Clinical Nutrition*, 2005; 59, 419–425) given as a support clearly concludes that: *Even though BMI z-score is optimal for assessing adiposity on a single occasion, it is not necessarily the best scale for measuring change in adiposity, as the within-child variability over time depends on the child's level of adiposity.* ***Better alternatives are BMI itself or BMI %.***	Replace BMI SDS by BMI or BMI % in the full document. Comment: *It was decided at the Ad Hoc Experts Group Meeting that in order to provide an internationally acceptable definition it was felt that in the European Guideline one should use the terms and definition proposed by T. Cole[1] for both child overweight and obesity. This author linked the accepted adult cut off points – a body mass index of 25 kg/m^2 for overweight and 30 kg/m^2 for obesity - to body mass index (BMI) centiles for children and so doing, proposed a construct bridging cut off points for children. When averaging data from Brazil, Great Britain, Hong Kong, Netherlands, Singapore and United States, he was able to create "international" cut off points for BMI for children from 2 to 18 years old. This approach was accepted by the Group and considered an appropriate way to solve the delicate problems, both of definition (terms) and growth standards (reference curves).* *In light of external comments, additional questions were posed to these Experts in May 2008 with a view to distinguishing between measures relating to definition of obesity i.e. cross-sectional work and measures of adiposity change i.e. longitudinal work. In line with the responses received, it was decided that the cut-off points derived by Cole in 2000 would remain the reference dataset for the Guidance document and that while the primary efficacy endpoint would remain the BMI SDS, that change in adiposity of the course of studies should also be measured and reported in terms of BMI and BMI% as follows:* *'It is recommended that the primary endpoint is a change in BMI Standard Deviation Score; however, change in adiposity should also be measured in BMI (%) units[4']*

[1] Cole T, Bellizzi MC, Flegal KM, Dietz WH; Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000; 320; 1240.

		The accompanying reference is to the Cole 2005 paper referred to in the comment received.
Lines 28-32	If BMI SDS is kept, its definition differs from WHO and from IOTF, as it can be read in the papers by Wang (*International Journal of Paediatric Obesity*, 2006; 1: 11-25) and Lobstein (*The International Association for the Study of Obesity. Obesity Reviews*, 2004, 5, Suppl. 1, 4-85).	Please, clarify by giving the exact definition/mode of calculation. Comment: See previous.
Lines 30-32	This seems consistent with what is written in the adult guideline, but is expressed differently to the FDA (draft) guidance. It is important for the conduct of global clinical trials that there is consistency in definitions.	Comment: Disagree – see previous re. internationally accepted definition from approach of Cole et al BMJ 2000.
3. AGE CLASSIFICATION		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Lines 49-54	Age grouping is not the only grouping that may be considered. It may be useful to look at those children still growing versus those who have reached their adult height. In the group which is still adding height it becomes the change in BMI that may be important, not just weight stabilization or weight loss (§ 4), or BMI SDS (§ 5), especially during the growth spurt of puberty where there is substantial addition of height to the child's stature as a primary endpoint. This group may overlap both the 6-10/12 and the adolescent group (10/12-18).	Comment: Agree. The following two categories are now used to define subgroups of the paediatric population: 1.Pre-pubertal and 2. Post-pubertal, categorised as follows: 1. Pre-pubertal: age 6 years old to onset of puberty as defined by a Tanner stage of 2. 2. Post-pubertal: post-puberty to age 18 years Due to the proposed length of the required studies and the difficulty in controlling for confounding relating to the growth spurt, it was decided that pubertal children need not be included in the studies to determine efficacy. It is recognised in the guideline that some pre-pubertal children may enter puberty during the clinical trial.
Lines 51-54	Puberty will confound the results. During puberty in girls the fat amount increases while in boys the fat mount decreases. In the draft guideline this issue has been monitored by categorizing the children to two categories younger children (6 years to 10 years or puberty for girls and to 12 years or puberty for boys) and adolescences 10 years or puberty to 16/18 years. This issue can be taken care of by focus on the growth spurt of puberty. It is therefore recommended using the suggested limit of puberty instead of age. For young children prepubertal over 6 years (Tanner stadium 1) The second group, adolescents but in	It is suggested to amend as follows: 1. Young children: age 6 years or older and **prepubertal** 2. Adolescents **in puberty** (Tanner stadium II-IV in boys and Tanner stadium II-V in premenarche girls). 3. Adolescents **in late puberty** (Tanner stadium IV-V and growth velocity of less than 1.5 cm/year last 12 months) Comment: Comment has been incorporated in revised wording – see previous comment.

	puberty (Tanner stadium II-IV for boys and Tanner stadium II-V but premenarche). A third group can be added that is adolescence in late puberty with growth velocity of less than 1.5 cm/year during the last 12 months. By this categorization it is easier to interpret the results from studies since the confounding from growth spurt in puberty is under control. Prepubertal children will have a more or less constant growth velocity and this also the situation for those in late puberty since the growth has ceased and final height is more or less reached.	
Lines 51-54	The FDA (draft) guidance suggests that initial studies are limited to adolescents (12-16 years), this seems a sensible approach that should be adopted also in the European guidance.	**Add:** …lifestyle modification only. **Initial studies should be limited to adolescents only unless otherwise justified.** Comment: Disagree – Ad-Hoc Experts agreed that there is a necessity to conduct separate trials in children and in adolescents. The results from studies in adults cannot be extrapolated to adolescents, nor can data from adolescents to younger children.
Lines 55-56	For children 2 to 6 years old, lifestyle modification only is recommended.	Please, clarify if it is an "automatic" age class waiver with no need for specific development in the PIP. Comment: The concept of age class waivers is outside the remit of this guideline and instead is a responsibility of the PDCO.
4. TRIAL POPULATIONS		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Lines 60-62	There are clear ethnic differences in response to some weight loss therapies (CB1 antagonists where Afro Americans have less weight loss)	**Modify:** …be extrapolated to the European population ~~since efficacy in terms of weight loss is~~ **where it is established that the response to the therapy** is not dependent on any ethnic background. Comment: Agree: Comment incorporated into final text: *'Study results from weight loss trials outside Europe could, however, be extrapolated to the European population where it is established that the response to the therapy is not dependent on any ethnic background'.*
Lines 62-65	*'Lifestyle factors may, however, have an important effect on efficacy in that a drug may be more effective in some populations*	Replace the sentence by requirements for standardizing the Non-pharmacological interventions, such as in lines 124-125:

	with, for example, a low degree of physical activity and this should be considered in performing trials. This sentence does not bring any clarity and could be misinterpreted.	*Non-pharmacological interventions (lifestyle changes, dietary manipulation, physical activity etc.) should be standardised and remain unchanged during all three phases of the study.* Comment: Disagree. Saying different things.
Line 71	The long run- in period requirement seems excessive and needless, particularly if adolescent patients are included which already have an obesity related disease such as hypertension or diabetes.	Comment: As previously stated, there is no intention of omitting the run-in period at present until such time that data suggests otherwise. Study design of anti-obesity drugs will be kept under review with emerging data.
Line71	We agree that a course of lifestyle intervention is the first step in the treatment of obesity. However, prior to entering a pharmacotherapy study, most patients will have undergone a number of lifestyle interventions with verifiable failure to meet treatment goals. Documentation of a history of a non-pharmacological intervention should be sufficient to demonstrate failure of the first-line therapy and qualify patients for a pharmacotherapy clinical trial. We agree that a well-defined lifestyle intervention should be implemented in all treatment groups. While a change in lifestyle intervention may very well results in a small additional decrease in BMI SDS compared to the regimen the patient was on prior to study entry, it is still possible to determine drug effect as the placebo-subtracted weight loss while on study drug. Therefore, it is not necessary to have an extensive run-in and achieve a new stable weight in order to assess the effect of study drug. Finally, as described elsewhere, dropout rates in obesity treatment studies are very high and can confound the analysis of treatment effect. Requiring a prolonged run-in phase will only exacerbate the problems of high dropout rate and will render the results of the study even less reliable. In summary, a run-in phase is not necessary to document treatment failure with the first-line treatment of lifestyle intervention or to determine the effect of study drug and will only worsen the problem of high dropout rates in chronic treatment studies.	We suggest that the requirement for a run-in period of 3-6 months be eliminated. A requirement that study subjects have a documented failure of first-line therapy of lifestyle intervention could be added. If the sponsor intends to do studies in treatment-naïve subjects, the requirement of a course of lifestyle intervention could be met by a run-in but it should not be required for patients who have already undergone one or more courses of first-line therapy without achieving a target BMI SDS. Comment: See previous. Also a 7 day period is too short to establish meaningful alterations in behaviour such as dietary intake or exercise.

Line 71	Notwithstanding the above comments and suggestion a short run-in period of 7 days prior to drug randomisation would be considered to be more appropriate than a long run -in due to the following reasons: • Simultaneous initiation of a non-pharmacological weight loss program (NPP) and drug treatment more closely mimics current clinical practice for obesity and provides a more accurate baseline for the clinical trial. Importantly, the simultaneous initiation of both the non-pharmacologic and drug interventions will allow for a more meaningful/consistent base line measure of related cardiovascular risk factors, changes in which are important secondary efficacy measures of drug treatment. • Elimination of patients during a placebo weight loss run-in introduces bias (by eliminating some subjects) and reduces 'generalisability' of the study results. • A similar approach has been recently used in several large weight loss adult trials designed by leading experts and sponsored by governmental agencies. • The traditional placebo run-in period was used to eliminate potentially non-compliant patients. We believe that a 7-day run-in prior to randomisation will achieve this goal. In addition, this approach will maximize the weight loss across all arms during the treatment phase of the trials, which should translate into further improvement in retention. • The combined effects of the drug and the non-pharmacologic intervention are additive, and the treatment differences between non-pharmacological intervention and combined non-pharmacological and pharmacological interventions are generally consistent across trials for a given agent, once maximal weight loss is achieved. Therefore, it is expected that the primary outcome of placebo subtracted weight loss at the end of the study would be the same with or without a	Comment: Disagree – see previous.

	placebo run-in period. In any event there should be flexibility in relation to the need for and duration of the run-in to adapt to the specific trial design.	
Section 4.3 (lines 84 to 91)	This section is vague and provides sponsors with little insight as to what will constitute an appropriate evidentiary requirement for product registration. We propose that the guidance needs to be more specific about measures considered medically meaningful for weight loss, preventing regain, or maintaining a current weight.	Comment: Disagree – section is only stating general goals.
Lines 88-89	*'Treatment goals are composite and need to encompass … the* ***presence of associated co-morbidities****.'* At line 115, it is stated that *"subjects suffering from severe co-morbidities be excluded from pivotal studies."*	Please, specify the co-morbidities/level of severity that may be included and those to be excluded according to the trial type (pivotal / non pivotal.). Comment: this is addressed in the following line 116 i.e. *'This is because these severely obese children may require more intense medical management than is available in clinical trial conditions.'* Severity may, therefore, be defined based on requirements for additional therapies.
Lines 98-99	*'It is recommended that* ***separate trials*** *for younger children (6 years to puberty) versus adolescent children (puberty to 18 years) are performed.'* It should be possible to perform a single study stratified by age subgroups. Furthermore, request for separate trials seems to be in contradiction with lines 108-109.	Please remove this sentence. Comment: Disagree – see previous comments on need for separate trials in pre-pubertal and post-pubertal subgroups.
Section 4.4 Lines 104-105	'(*they no longer fulfil the definition of obesity)'*	Please amend: ***(*****if*** *they no longer fulfil the definition of obesity*) Comment: Agree. Text amended as proposed.
Lines 108-109	*'Children of* ***all ages*** *should be* ***equally*** *represented in the study.'* Does this sentence refers to the two age subgroups that were described in §3 (lines 51-54) or to any requirement for stratification each year by year, the later rendering the trial not feasible.	Please delete the word "equally" so that the sentence reads as follows: *'Children of all ages should be represented in the study.'* Comment: Agree in principle. Page: 13 [0]Term 'equally' was softened so final text reads: *'Children of all ages should be represented in sufficient large proportions in the study.'*
Section 4.4 Line 120	Please see comment made for section 4.1 line 71	Comment: Disagree – see previous.

Section 4.5 Lines 123 and 129	*Trials should be randomised, double-blind,* ***placebo-controlled trials****.'* *'The treatment phase should last for* ***at least 1 year.'*** We question whether it is realistic to expect placebo-controlled trials of 12 months duration in the paediatric population. Most drugs will provide maximum weight loss by 6 months of therapy. Furthermore there are ethical concerns to leave paediatric patients under placebo treatment for 1 year, especially in those children who are >99% for BMI adjusted for age. There should be some earlier dropout or rescue therapy. It is critical to address the issue for the long term benefit of the child. An alternative design would be, responders could be rolled over into a prevention of regain study to evaluate long term exposure and efficacy.	Comment: The Ad-hoc Experts considered if it would be ethical to continue a placebo treatment in obese children for 1 year and the group found this approach acceptable.
Lines 134-136	To obtain 1-year data from patients who dropped out of the trial will only rarely be possible. Furthermore, it is difficult to understand the value of measuring body weight at the time when they would have completed the study. It is of course valuable to collect safety information.	The request to obtain 1-year data in patients who dropped out of the study should be dropped and the following sentence should be deleted. ~~If possible, patients who drop out from a 1-year study should have a body weight measurement at the time he or she would have completed the study after 1 year of taking part.~~ Comment: Disagree – see previous.
Line 138	The proposed observation phase after stopping drug therapy is considered to be too lengthy. Furthermore the percentage of patients that will be lost to follow-up is expected to be high. The observation phase should take into account the half-life of the drug. In general, drug effect (efficacy and/or safety) is related to systemic exposure. Since ~93-97% of drug quantity should be eliminated in 4-5 terminal elimination half-lives, there is a low likelihood that any effect would be attributed to the drug after that duration of time. In light of these concepts, a 6-month observation period following discontinuation of subjects from the study seems excessive unless the elimination half-life of the drug is very long (at least 1.2-1.5 months), or there is evidence that	*"It is recommended that the observation phase after stopping drug therapy should be appropriate based on the half-life of the drug."* Comment: Disagree – see previous, after discontinuation of treatment the patients should be followed to assess relapse and/or rebound.

	drug effect is not directly related to the time course of exposure.	
Line 137	Just as with any treatment for a chronic metabolic disease, discontinuation of obesity pharmacotherapy will be followed by relapse of obesity. If possible an observation phase should be implemented early in development to assess reversibility of any adverse clinical or laboratory effects which are observed. Just as it is not necessary to look for evidence of an increase in blood glucose after discontinuation of insulin in patients with Type I diabetes mellitus, it is not necessary to look for evidence of relapse of obesity following discontinuation of pharmacologic or non-pharmacologic treatment of other chronic metabolic diseases such as obesity. While it is true that the younger the patient the less likely that obesity will persist into adulthood, maintenance of weight loss following discontinuation of pharmacotherapy is rare, and cannot be attributed to previous pharmacotherapy in those rare patients in which weight loss is maintained.	An alternative approach could be that an observation period be required to assess reversibility of adverse effects in Phase 1 and 2 studies. The duration of the discontinuation should depend on the nature of the expected and observed adverse clinical and laboratory effects and the duration of action of the drug (which might be quite long with large- or small-molecule compounds with long half-lives). Therefore the duration must be individualized to the individual compound. If the reversibility of adverse effects is adequately evaluated in Phase 1 and 2, there should be no requirement in Phase 3. Comment: Disagree – see previous, after discontinuation of treatment the patients should be followed to assess relapse and/or rebound.
Line 146	We agree that body composition analysis is necessary in a subset of study subject to document the fat loss associated with weight loss. However, there are a number of currently or potentially validated methodologies which could be used, including hydrostatic weighing, 2-, 3- and 4-compartment models, air displacement plethysmography, and emerging technologies which do not involve ionizing radiation such as quantitative nuclear magnetic resonance (qNMR).	We suggest that any validated body composition methodology be appropriate to ensure that any weight reduction is associated with reduction in fat and not lean body mass. Comment: Agree. Final wording: *'Body composition analysis using a validated methodology is necessary in a representative sample of trial patients to ensure that any weight reduction is caused primarily by a reduction in fat content and not lean-body mass.'*
5. ASSESSMENT OF EFFICACY OF NEW MEDICINAL PRODUCTS FOR THE TREATMENT OF OBESITY IN CHILDREN		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Line 150	It is not clear which cut-off is proposed, a BMI SD score corresponding to an adult BMI of 30? Is there a rational for this? The cut-off does not seem to be based on the future risk of CHD (NJEM 357; 23, 2329-37). Are there good data on BMI SD score in relation to T2D or IGT?	Comment: see previous comments re. definition of obesity.
Line 150 to 152	The current wording implies that change in BMI SDS should be used as the primary endpoint. Other assessments such as DEXA measurement,	Comment: see previous comments re. primary efficacy endpoint.

	waist circumference could be used as the primary endpoint. Therefore, the choice of primary endpoint should be justified by the applicant.	
Lines 151-152	*'In adults a **10% weight reduction** is accepted as a positive endpoint.'* Great emphasis is made in this addendum on the choice of a primary endpoint that is specific to the paediatric population, following the discussion in §2 for the definition of obesity in children (see also our comment for lines 28-32, above.) Therefore, definition of clinical significance using this adult-based 10% weight loss of baseline weight is inconsistent. Furthermore, it contradicts statements in §4.3 (lines 89-90): ***Halting** abnormal/excess **weight gain** or **decreasing** the **rate of weight gain** are important goals in paediatrics and could be primary endpoints.*	Restore consistency with §2 and §4.3 by providing any definition of clinical significance in the same unit. Comment: issues relating to definition of obesity and endpoints have been previously addressed.
Lines 151-152	Where adults are quoted it should be consistent with the adult guideline i.e. at least 5-10% of initial weight, weight loss at least 10% of baseline weight which is also at least 5% greater than that associated with placebo. For paediatrics it is also important to keep the sentence on line 152, i.e. however the degree of change should be justified by the applicant.	Amend: …as described in the definition of obesity in children above and at least 5-10% of initial weight, weight loss at least 10% of baseline weight which is also at least 5% greater than that associated with placebo. Clarify: How the degree of change should be justified by the applicant. Comment: The degree of change that is applicable to adults is not applicable to children. Allowing the degree of change to be justified by the applicant allows for flexibility.
6. ASSESSMENT OF SAFETY OF THE NEW MEDICINAL PRODUCTS FOR THE TREATMENT OF OBESITY IN CHILDREN		
Line no. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Lines 169-170	*Although **self-esteem** could fall under the efficacy category it is more appropriate to monitor it as a safety issue.* To consider self-esteem as an adverse event (as well as an efficacy criterion or as a lack of efficacy criterion) is very arbitrary, unless considering it with its entire context as listed globally in lines 167-169.	Remove this sentence or give the rationale for isolating this parameter. Comment: The final wording is: *'Although self-esteem could fall under the efficacy category it is more appropriate to monitor it as a safety issue.'*