

**SUBMISSION OF COMMENTS ON**

**Guideline on Similar Biological Medicinal Products containing biotechnology derived products as active substance:**

**non-clinical and clinical issues Annex: Somatropin (EMA/CHMP/94528/05)**

**Doc. Ref: EMA/89166/2006**

**COMMENTS FROM**

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**GENERAL COMMENTS**

Quality issues will be addressed in a separate guideline.

A section on Reference Medicinal Product should be included to harmonise with the Guideline on Similar Biological Medicinal Product (CHMP/437/04) and Quality issues (CHMP/49348/05) guidelines

Each applicant developing a new rh-GH must identify in advance a single reference product to which similarity is claimed. The same reference product must be used at each stage of the development process, including establishment of specifications for product quality, as well as non-clinical and clinical studies.

On a related matter the guidance does not describe which product(s) should be used as comparator product(s). Since the formulations, pharmacokinetics, dosages and reported efficacy among existing Somatropin products can vary greatly which product should be used as a comparator product in all preclinical and clinical testing?

**SPECIFIC COMMENTS ON TEXT**

**GUIDELINE SECTION TITLE**

<b>Line no<sup>1</sup>. + paragraph no.</b>	<b>Comment and Rationale</b>	<b>Proposed change (if applicable)</b>
<b>1. Introduction</b>	Different somatropins with identical amino acid sequence and produced by recombinant technology using E. coli, mammalian cells or yeast cells as expression system are available. All these may be used as comparator or only dependent on the host cell of the biosimilar?	The use of a different expression system per se would not preclude the assumption of 'biosimilarity'
<b>3.1</b>	"In order to assess any alterations in reactivity.."	Redundant

<sup>1</sup> Where available

<b>Pharmacodynamics studies</b>	Add “and any differences in activity”	
<b>3.2. Toxicological studies</b>	Comparative toxicological studies? At least one species for repeated toxicology and local tolerance studies required. Why?	Assuming “analytical” comparability of new rhGH and reference medicinal product (RMP) and taking into account published data concerning non-clinical toxicity of hGH, the proposed non-clinical toxicological program has been substantially reduced in comparison with the “standard” program requested for new active substances. It consists of one comparative, 4 week, repeat dose toxicity study and one comparative local tolerance study, which may be performed, if feasible, as part of the repeat dose toxicity study. This program is designed to provide: (i) information, as part of the overall comparability exercise, whether the non-clinical toxicological properties of new rhGH and RMP are comparable (ii) assurance that no “unexpected toxicity” (e.g. toxic effects induced by process-related impurities) will occur after application of the new rhGH to humans. “Unexpected toxicity” cannot be excluded with sufficient certainty on basis of quality data alone, however, should be checked before starting clinical development. The proposed non-clinical toxicological program is considered suitable to provide the required information and should be a part of the standard development program for a new rhGH
<b>4.1 Pharmacokinetic studies (clinical)</b>	Absolute requirement for suppression of endogenous GH production Patients should be also balanced for type of gene defect because this influences immunogenicity	Preferable but no absolute requirement. Both have been accepted in the past.  GH gene deletion is a very rare condition. Therefore such patients are unlikely to be included in the clinical trials. Applicant should provide information on reason for GH deficiency which will be taken into account when interpreting results
<b>3.1 Pharmacodynamics studies</b> <i>In vitro</i> studies:	I would suggest that these studies might be conducted in parallel to clinical PK studies depending upon the level of analytical comparability, stability data, and other process development studies showing good process consistency and reproducibility of product parameters. That is, one may take a 'confirmatory' testing path in parallel to PK studies if the data warrants it. This logic follows the same approach used currently for US comparability studies and some EMEA Type I Variations in which the analytical data support continued clinical use.	The whole comparability exercise is a stepwise procedure starting with the comparison on quality grounds then proceeding to non-clinical and clinical studies. At each step a decision will need to be made as to whether the “biosimilar” path should further be pursued. Therefore, <i>in vitro</i> studies will usually precede <i>in vivo</i> studies.
<i>In vivo</i> studies	I would recommend this study be performed on a lot that is representative of the process used to make clinical supplies for PK or safety studies. If this is tested on a pilot scale lot, this may be suitable as a one-time test, provided the analytical comparability of material from pilot scale to proposed commercial scale is supportive. That is, this testing does not have to be repeated for each level of production when the comparability data are supportive. It may be more meaningful to have side-by-side stability studies against a reference lot.	All pivotal studies should preferably be performed with the final formulation from the final manufacturing process. Otherwise sound justification will be and additional data may be needed to make sure that the results obtained with a previous formulation are applicable to the formulation intended for marketing.
<b>3.2 Toxicological studies</b>	I do not think these studies are automatically warranted for a biosimilar growth hormone product when the analytical comparability and hypophysectomized rat studies are supportive of comparable activity. Toxicology studies should be reserved for those situations where data are ambiguous or the method of manufacture is so novel (e.g., bioengineered plant-derived GH) as to warrant a full preclinical program.	Assuming “analytical” comparability of new rhGH and reference medicinal product (RMP) and taking into account published data concerning non-clinical toxicity of hGH, the proposed non-clinical toxicological program has been substantially reduced in comparison with the “standard” program requested for new active substances. Therefore, safety pharmacology, reproduction toxicity, mutagenicity and carcinogenicity studies are not routine requirements for a “biosimilar” rhGH and only one repeat dose toxicity study of limited (4 week) duration is requested, instead of chronic studies in two different species. Furthermore, if feasible, the proposed local tolerance study may be performed as

		<p>part of the described repeat dose toxicity study.</p> <p>As is stands, the proposed non-clinical toxicological program is designed to provide:</p> <p>(i) information, as part of the overall comparability exercise, whether the non-clinical toxicological properties of new rhGH and RMP are comparable</p> <p>(ii) assurance that no “unexpected toxicity” (e.g. toxic effects induced by process-related impurities) will occur after application of the new rhGH to humans. “Unexpected toxicity” cannot be excluded with sufficient certainty on basis of quality data or <i>in vivo</i> pharmacodynamic animal data alone, however, should be checked before starting clinical development.</p> <p>Therefore, the proposed non-clinical toxicological studies should be a part of the standard development program for a new rhGH.</p>
	<p>A tolerance study should be applied as part of a testing algorithm for when there are substantial or questionable differences in sponsor versus reference standards/products. I would not stipulate this as an automatic requirement.</p>	<p>As part of the proposed non-clinical toxicological program, the requested local tolerance study is designed to provide:</p> <p>(i) information, as part of the overall comparability exercise, whether the local toxicological effects of new rhGH formulation and reference medicinal product (RMP) are comparable</p> <p>(ii) assurance that no “unexpected local toxicity” (e.g. toxic effects induced by process-related impurities) will occur after application of the new rhGH formulation to humans. “Unexpected toxicity” cannot be excluded with sufficient certainty on basis of quality data alone, however, should be checked before starting clinical development.</p> <p>It should be mentioned that the presence of substantial differences between new rhGH and RMP, as referred to in the submitted comment, would normally be expected to preclude a further development of the new rhGH as a similar biological medicinal product.</p>
<p><b>4.3 Clinical efficacy studies</b></p>	<p>Instead of an automatic requirement for clinical efficacy studies, I would recommend the sponsor perform a safety study in GH-deficient adults to evaluate PK and safety. This approach has been used by FDA in discussions with US-based sponsors developing biosimilar GH products.</p> <p>The primary reason for this is that if a sponsor has shown by virtue of analytical comparability, <i>in vivo</i> studies (e.g., hypophysectomized rat model), side-by-side stability studies, and bioequivalence in a PK study using adult GH-deficient subjects - then the critical aspects of comparability have been largely addressed and this open-label study should be devoted to evaluating safety in a larger patient population.</p> <p>The requirement for a double-blind, randomized clinical study to demonstrate clinical efficacy against a reference standard (e.g., marketed product) may require a much larger study than the original sponsor used to gain market approval.</p>	<p>For the time being, analytical characterisation and a limited non-clinical programme alone cannot establish therapeutic equivalence of a similar biological medicinal product with the reference product. In addition, IGF-1 is no established surrogate marker for efficacy. Therefore, a clinical equivalence trial in a sensitive model is necessary. GH deficient children are the preferred models because they are GH sensitive and represent the classic indication for GH therapy for which most experience has been gathered and for which equivalence margins may be easiest to define. However, a study in GH deficient adults is principally possible.</p> <p>The voiced fear that the requirement for a comparative clinical trial is a major development obstacle is not confirmed by real life experience. In this respect it should be pointed out that the applicant of a ‘biosimilar’ rHuGH will need to perform only one rigorous comparative clinical trial in one indication with the possibility of extrapolation to the other indications of the reference product.</p>
	<p>4.1 Pharmacokinetic studies</p> <p>Why is C<sub>max</sub> and T<sub>max</sub> not required?</p>	<p>C<sub>max</sub> and T<sub>1/2</sub> have been included as a secondary endpoint. T<sub>max</sub> is not considered a relevant parameter.</p>
<p><b>Introduction</b></p> <p><b>Paragraph 2</b></p>	<p>In the last sentence of the second paragraph a typo should be corrected: the product-related substances/impurities may occur in deamidated and oxidised forms. The sentence should therefore read:</p> <p>“Several techniques and bioassays are available to characterise both the active substance and product-related substances/impurities such as deamidated and</p>	<p>Will be corrected</p>

	oxidised forms and aggregates	
<b>Non-clinical studies</b>	<p><b>3.1. Pharmacodynamic studies</b></p> <p><b><i>In vivo studies</i></b> We propose changing the sentence accordingly:</p> <p><b><i>“Only if the results of the in vitro studies performed with validated comparative bioassays are not satisfying, an appropriate in vivo model (e.g. the weight gain assay and/or the tibia width growth assay in immature hypophysectomized rats; data may already be available from quality-related assays) should be used to quantitatively compare the pharmacodynamic activity of the similar biological medicinal and the reference product.”</i></b></p>	<p>The comparability exercise is a stepwise procedure. While the proposed <i>in vitro</i> pharmacodynamic studies (e.g. receptor-binding and cell proliferation studies) are designed to prove comparable affinity/agonistic activity of new rhGH and reference medicinal product (RMP) at the GH receptor, the <i>in vivo</i> pharmacodynamic studies provide additional information about comparability of their pharmacokinetic properties. This reflects the fact that pharmacodynamic activity <i>in vivo</i> is dependent both on receptor affinity and on availability of the rhGH in the receptor compartment(s) in different tissues, which in turn is related to pharmacokinetic parameters such as absorption, tissue distribution, metabolism and excretion.</p> <p>Therefore, the proposed <i>in vitro</i> and <i>in vivo</i> pharmacodynamic studies provide complementary information about comparability of new rhGH and RMP and should thus both be part of the standard non-clinical testing program.</p> <p>Additional comment: since at each step of the development program a decision will need to be made as to whether the “biosimilar” path should further be pursued, the presence of substantial differences between new rhGH and RMP in the <i>in vitro</i> bioassays, as indicated by the wording that “studies performed with validated comparative bioassays are not satisfying”, would normally be expected to preclude further development of the new rhGH as a similar biological medicinal product</p>
<b>3.2. Toxicological studies</b>  <b>Paragraph 1</b>	<p>The last sentence in the first paragraph requires that special emphasis should be laid on the determination of immune responses in toxicological studies. This is in strong contradiction to the “Guideline on Similar Biological Medicinal Products containing Biotechnology-derived Proteins as Active Substance: Non-Clinical and Clinical Issues (EMA/CHMP/42832/2005) which states under item 6. Immunogenicity , Principles for evaluation of immunogenicity in the second sentence: “Normally an antibody response in humans cannot be predicted from animal studies.”</p> <p>Additionally it must be taken into account that presently there is no non-clinical testing system available capable of predicting, from a scientific point of view, whether a new product will cause immunologic consequences. Conclusions about the immunogenicity of hGH are therefore very difficult to draw from pre-clinical studies and must be evaluated through clinical assessment.</p> <p>We therefore propose the deletion of the following sentence in its entirety: In this context, special emphasis should be laid on the determination of immune responses.</p>	<p>Non-clinical toxicological studies are part of the overall comparability exercise. Since immunological mechanisms are expected to be able to detect even subtle structural differences between new rhGH and reference medicinal product (RMP), special emphasis should be laid on the characterization of differences in immune response after administration of new rhGH and RMP to laboratory animals within the context of the requested repeat dose toxicity study.</p> <p>In conclusion, determination of immune responses in non-clinical toxicity studies constitutes an important component of the non-clinical comparability exercise, however, is not aimed (resp. not suitable) to predict antibody response in humans.</p>
<b>4.3. Clinical efficacy studies</b>  <b>Paragraph 2</b>	<p>The first sentence in the second paragraph contains a typo and should be corrected to read as follows:</p> <p><i>“Sensitivity to the effects of somatropin is higher in GH-deficient than non-deficient conditions.”</i></p>	Will be corrected
<b>4.3. Clinical efficacy studies</b>  <b>Paragraph 5</b>	<p>The final sentence requires that <i>‘the recommended duration of the comparative phase is at least 6 months and may have to be up to 12 months’</i>.</p> <p>We wonder why the comparative phase for the clinical efficacy trial has to last so long (up to 12 months) for this product, whereas for the other product specific guidelines a comparative efficacy phase for a maximum of only 6 months is</p>	For proper assessment of growth at least 6-month data and ideally 12-month data are required due to the measurement errors inherent in short-term growth measurements and significant variability in short-term growth. Because of additional seasonal variability in growth, 12-month data would be ideal.

	required.	
<b>Section 5. Clinical safety</b> <b>Paragraph 1</b>	<p>The draft guideline requires that comparative immunogenicity data of patients who participated in the efficacy trial should be provided at 3-month intervals for 12 months. This is in contradiction to the text in paragraph 5 of the clinical efficacy studies, which states that "the recommended duration of the comparative phase is at least 6 months and may have to be up to 12 months."</p> <p>Accordingly, this inconsistency should be clarified and the sentence should be changed to be in line with the text in previous parts of the draft guideline:</p> <p><i>"The applicant should provide comparative immunogenicity data of patients who participated in the efficacy trials for <del>12</del> at least 6 months, and where appropriate, for up to 12 months, at 3-month intervals, using validated assays of adequate specificity and sensitivity."</i></p>	<p>The applicant is given the choice to define his primary efficacy endpoint for the 6-month or the 12-month time point. This may have implications for the sample size or the time point of application for marketing authorization. Nevertheless, 12-month immunogenicity data will be required pre-authorisation because anti-GH antibodies usually develop during the first 9 to 12 months of treatment.</p>
	<p>We have concerns regarding the use of the term "comparability" throughout these guidelines. We strongly feel that "comparability" should be restricted to pre- and post-change comparisons within a single, well-defined manufacturing process, as has been the case historically (see ICH Q5E), rather than referring to comparisons between two different manufacturing processes, as is the case for biosimilar and reference products</p>	<p>We believe that by issuing separate guidelines for changes in the manufacturing process and for similar biological medicinal products this difference is made clear. Nevertheless, a comparability exercise has to be performed to demonstrate the similar nature of two biological medicinal products</p>
	<p>We understand that although the guidance concerns somatotropin, it would also be relevant to mecasermin (rhIGF-1). Apparently because somatotropin has been approved for a number of different indications, Section 4.3 (Clinical Efficacy) begins by discussing equivalent therapeutic efficacy. We understand that the guidance would also be relevant to new indications for mecasermin for which there has been no previous regulatory approval in the European Union.</p>	<p>For biologicals without a reference product approved in the EU the 'biosimilar' route is not possible according to legislation.</p>
<b>Section 4.3</b>	<p>Comments regarding Section 4.3 in the order of the guidance test are as follows:</p> <p>"..., at minimum the person performing height measurements should be masked to treatment allocation." At small study centers, there may be few staff adequately trained to measure heights accurately and these same staff will be aware of the treatments being administered. In such centers, the inaccuracies introduced by this staff not being masked are likely to be less than the inaccuracies that would be introduced by having less well-trained staff (who are masked to treatment) measure heights. Thus, while measurement of height by staff who are masked to treatment is to be encouraged, it should not preclude height measurements by appropriately trained personnel.</p>	<p>The sponsor of the trial has to ensure that the staff involved is appropriately trained and that height measurements are performed in a scientific and standardized manner</p>
<b>Section 4.3</b>	<p>"Study subjects should be pre-pubertal before and during the comparative phase of the trial ...". While it is agreed that subjects should be pre-pubertal at baseline, they should also be past infancy, e.g., at least 3 years old at baseline. In addition, there will be a negligible effect on the interpretation of the results of the study if a small number of subjects enter puberty during a study of up to one year in duration. Hence, we suggest that the guidance simply recommend that study subjects should be at least 3 years old and prepubertal at baseline. One may also put a limit on the bone age for females (11 years) and for males (12 years) so that the expected number of subjects entering puberty during the course of the study would be small.</p>	<p>The pubertal growth spurt is a confounding factor in the assessment of the growth response to GH. Therefore, patients should remain prepubertal during the comparative phase of the study. One reasonable approach would be to limit the age/bone age at baseline for eligibility. In this respect, the proposed bone age of 11 years for girls would be too high since girls experience their growth spurt usually at the start of puberty. It is agreed that single cases of onset of puberty during the study may not affect the overall conclusions from the study but this has to be decided on a case by case basis. Variability in growth is least between the age of 6 and 10 years. Both treatment groups should be balanced with regard to age and gender.</p>

	Note also that girls get their pubertal growth spurts earlier in puberty than boys, so having a boy in early puberty is less problematic than a girl.	
<b>Section 4.3</b>	<p>“It is important that the study groups are thoroughly balanced for baseline characteristics ...” The only known way to achieve such balance with reasonable sample sizes is through the use of baseline adaptive randomisation methods, which are discouraged by the CHMP (<a href="http://www.emea.eu.int/pdfs/human/ewp/286399en.pdf">http://www.emea.eu.int/pdfs/human/ewp/286399en.pdf</a> ). While baseline adaptive randomisation should be allowed and in some instances even encouraged rather than discouraged, we suggest rather that the combination of the selection of an appropriate subject population as discussed in (2) above together with the selection of an appropriate efficacy endpoint as discussed in (4) below greatly reduces the concern for balance in baseline characteristics.</p>	We believe that in the statistical model only well-established factors influencing outcome should be included. Knowing that age and gender are important factors we still feel that the use of standardized scores (that adjust for age and gender) are preferable.
<b>Section 4.3</b>	<p>The opposite problem exists in the use of height standard deviation scores. The standard deviation for height for boys 3 years old is about half that of the standard deviation for height for boys 11 years old (e.g., <a href="http://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf">http://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf</a>). Thus, the increase in height standard deviation score is notably less in older prepubertal subjects than in younger subjects.</p>	<p>In addition, as opposed to e.g. height SDS the change in height velocity SDS is standardized. Height velocity is also an acceptable primary endpoint but in this case it is even more important that treatment groups are well balanced for age and gender</p>
<b>Section 4.3</b>	<p>Because the baseline height velocity is not highly correlated with the on-treatment height velocity, the variance of change in height velocity is notably greater than the variance of the on-treatment height velocity. Therefore, if change in height velocity is used as an endpoint, then the baseline height velocity should be used as a covariate (or equivalently, the on treatment height velocity should be the endpoint and the baseline height velocity should be used as a covariate “Consecutive height measurements should be standardized and performed at the same time of the day...” While heights can change as the day progresses, these differences are not generally very large and therefore unlikely to affect study conclusions. Similarly, it may not always be possible to have all height measurements made by the same person, particularly the height measured 6 to 18 months prior to baseline and it may not matter much who has done the height measurement as long as the measurement has been made professionally using methods that are consistent within study center. Thus, while consistency of time of day and person making the measurement should be encouraged in the guidance, such consistency should not be considered as an absolute requirement for all subjects at all times</p>	<p>The difference between heights measured in the morning and in the evening is often around 1 cm which would add to the variability caused by measurement errors inherent in short-term growth measurements and the variability of short-term growth. Every effort should be made to reduce the variability of the primary endpoint. This includes repeated and standardized measurements using a validated measuring device and measurements performed at approximately the same time of the day and by the same trained person during the comparative phase of the study. The guidance document does not state that height measurements before and during the treatment phase have to be performed by the same observer (although this would be ideal)</p>
<b>Section 4.3</b>	<p>“Equivalence margins must be justified ...” Yes, but it should be noted that appropriate equivalence margins will be dependent on the age of the subjects if either the change in height velocity standard deviation score or the change in height standard deviation score is used as the primary endpoint. On the other hand, if the change in height velocity is the primary endpoint (with age and baseline height velocity as covariates), then an equivalence margin can be determined that is independent of age.</p>	It is clear that the equivalence margin is dependent on the chosen endpoint. The equivalence margin has to be pre-defined and appropriately justified, primarily based on clinical grounds and taking into consideration the data obtained with the reference product.
<b>Section 4.3</b>	<p>“... taking into account assay sensitivity ...” This vocabulary seems to be peculiar to non-inferiority trials. It would be best to use vocabulary that is more readily understood, particularly when “assays” in the more commonly used sense (such as assays for growth hormone, IGF-1, IGFBP-3, and antibodies) play an essential role</p>	Will be reworded to clarify

	in a clinical study of a growth promoting agent. In addition, it is not clear how “assay sensitivity” should play a role in establishing the non-inferiority or equivalence margin. If one establishes the margin “primarily on clinical grounds” as recommended in the guidance, then the sponsor should design the study in such a way as to meet the stated agreed-upon margin and that margin should not be relaxed to accommodate either a small sample size or a larger standard deviation than the sponsor would like.	
<b>Section 4.3</b>	Regarding pre-treatment height velocities: “at least 6 months and may have to be up to 12 months” Even when height measurements are taken under controlled conditions in clinical trials, successive height velocities in untreated subjects are not highly correlated. Successive height velocities in treated subjects under controlled conditions are also not highly correlated. Moreover, pre-treatment height velocity and on-treatment height velocities are not highly correlated (especially after adjustment for age). Hence, while measurement of heights between 6 and 18 months prior to baseline is to be encouraged in order to have an accurate measurement of the baseline height velocity, the role played by baseline height velocity is not as critical as that of the on-treatment height velocity.	Baseline height velocity is an important factor in making the diagnosis of GH deficiency. Pre-treatment height velocity is usually lower and growth response to GH treatment usually higher in patients with more severe growth hormone deficiency. In addition, if change in height velocity or change in height velocity SDS is the primary endpoint; accurate assessment of baseline growth is absolutely necessary.
	In order to evaluate the degradation profile of somatropin products, an appropriate battery of analytical methods should be used to detect degradation products of somatropin. Reference should be made to the relevant EMEA and ICH guidelines for biotechnology products	Appropriate references are given in the general guideline and should not be repeated in the product-specific annexes
	Degraded somatropin (stored at elevated temperatures corresponding to accelerated end of shelf life) contains about 191 amino acid residues. Therefore the degradation products at the end of shelf life of a biosimilar somatropin product should also be subject to appropriate qualification tests.	Agreed but this is a quality issue and therefore is addressed in the quality guidelines
	Each applicant developing a new rh-GH must identify in advance a single reference product to which similarity is claimed. The same reference product must be used at each stage of the development process, including establishment of specifications for product quality, as well as non-clinical and clinical studies.	Agreed
	Ensure that any guidance on quality issues is developed independently of non-public proprietary data on reference products to ensure that the innovator's intellectual property rights are not undermined.	Beyond the scope of the guideline
	Introduction In Paragraph 3, the last sentence should read: “The same receptors are thought to be involved in all currently approved therapeutic indications of rhGHs”.	Agreed.
	Non-clinical studies As comparability studies should include description of split and degradation products occurring during shelf life, analyses should also include an evaluation of the efficacy and safety implications of any observed difference between the biosimilar product and the reference product. While this may be difficult to prove in clinical trials it should be addressed in non-clinical studies.	The comparability exercise is a stepwise procedure starting with the comparison on quality grounds then proceeding to non-clinical and clinical studies. At each step a decision will need to be made as to whether the “biosimilar” path should further be pursued. Therefore, while evaluation of safety and efficacy implications of split and degradation products occurring during shelf life appears in principle possible within the framework of the proposed non-clinical testing program, the presence of substantial differences in product quality between new rhGH and reference medicinal product may preclude further development of the new rhGH as a similar biological medicinal product.
<b>Non-clinical studies</b>	<i>"Any differences in the non-clinical data from the similar biological product compared to the reference product must be addressed with a focus on potential safety implications. Additional non-clinical studies may be needed prior to clinical</i>	In principle, agreed. However, since at each step of the comparability exercise a decision will need to be made as to whether the “biosimilar” path should further be pursued, the presence of <u>substantial</u>

	<i>studies if safety issues persist following a thorough assessment of the data".</i>	differences between new rhGH and reference medicinal product in the non-clinical studies would normally be expected to preclude a further development of the new rhGH as a similar biological medicinal product.
	<p>Clinical studies We believe that the guideline should explicitly state that it only covers the recommendations for children indications. Paragraph 1: As required by section 4 of Part II of Annex I to Directive 2001/83 amended, each indication for which similarity is claimed must be separately demonstrated in at least one appropriate clinical trial. The rationale behind the insistence on one clinical trial per indication can be justified because the risk of immunogenicity can be influenced by the baseline condition and the patient population. In consequence, an extrapolation of the adult immunogenicity result cannot be extrapolated into a paediatric population. Likewise between adult GHD and HIV in AIDS patients. We suggest modifying the following sentence: "Equivalent therapeutic efficacy between the similar biological medicinal product and the reference product should be demonstrated for each indication in a direct comparison in at least one adequately powered, randomised, parallel group, confirmatory clinical trial". An appropriate number of patients required in each efficacy study should be assessed, in order to ensure that the trials are adequately powered to objectively determine that: The endpoints were met; To take into consideration the existing experience with growth hormone products.</p>	<p>Part II, section 4 of the Annex I of Directive 2001/83/EC reads: "In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications." Therefore, extrapolation to other indications of the reference product is possible if appropriately justified. Since there is only one GH receptor and all actions of GH are thought to be mediated via this receptor, demonstration of similar efficacy and safety in a sensitive model (preferably in GH deficient children) may allow extrapolation to other indications of the reference product. We are not aware that immunogenicity is higher in the adult than in the paediatric population which would be of concern. HIV and AIDS are no approved indications for GH treatment in the EU.</p>
<b>Paragraph 2:</b>	<p>4.3 Clinical studies The draft Annex Guideline states "<i>Subjects should be pre-pubertal before and during the comparative phase of the trial to avoid interference of pubertal growth spurt with the treatment effect</i>". It seems that instead of including only pre-pubertal subjects during the comparative period, it is preferably that "<i>subgroup analysis should be performed to determine the effect of puberty, should subjects included enter puberty during the comparative phase of the study</i>".</p>	If puberty occurs during the comparative phase the concerned patients may have to be excluded from analysis to avoid confounding effects
	<p>4.3 Clinical studies As pointed out, the sensitivity of the population to the effects of the Somatropin justifies the need of conducting a clinical trial for each specific indication. In addition the origin of the disease could be different in GH-deficient versus non-GH deficient conditions. Overall, the same level of requirements related to the methodological aspects should be applied to the biosimilar rh-GH product than to the reference product.</p>	<p>The most sensitive model should be chosen for the comparability exercise since it is most likely to detect differences in efficacy and safety between the 'similar' and the reference product. (also see comment above).</p>
	As far as the receptors are concerned, it cannot be excluded that a substantial difference would result in a different behaviour at the receptor site when comparing with the reference growth hormone. The present experience with different growth hormone formulations demonstrates, that if a new molecule has a different receptor binding profile, this could lead to different efficacy and safety and it is paramount to explore further.	Since there is only one GH receptor, a different receptor binding profile of clinical significance would become evident in the clinical equivalence trials.

	<p>Growth hormones act through GH receptors and there are indeed differences depending on the indication. The receptor varies in abundance of sensitivity (e.g., where Turner syndrome girls need more GH than GHD patients and within the GHD patient group, men need less GH than women depending on the estrogen state since estrogen affects the GH level in the liver). Also, the receptor elicits different properties/signalling in different tissue (e.g. it affects the growth plate (bone/chondrocyte) in children, muscle tissue in AIDS-wasting, fat tissue in HARS. Therefore, the response to treatment depends on the dose, the target tissue and indication.</p>	<p>We agree that the treatment response depends on dose, target tissue and indication. However, there is only one GH receptor and all actions of GH are thought to be mediated via this receptor. E.g. the way how GH brings about growth is independent of the reasons for growth disturbance</p>
<b>4.3 Clinical studies</b>	<p>If validated measuring devices are used together with standardised height measurements, as required in the text, it is unclear why consecutive height measurements need to be carried out by the "same observer".</p>	<p>There may be considerable inter-observer variability in height measurements. Therefore, the same person should measure the same child for the duration of the comparative phase of the study, whenever possible</p>
<b>Paragraph 4:</b>	<p>With respect to study duration, final height data for each indication and as much safety data as is feasible are expected for the currently available branded rh-GH products. Studies are therefore lengthy, expensive and logistically difficult to implement and maintain. In the interest of the patients, it is essential that biosimilar products are not subject to less rigorous requirements than are applied to innovator products. Therefore, the recommended duration of the study comparative phase should be 12 months, in line with the minimum requirements that are required to the innovator company. EBE members suggest changing the sentence as follows:  <i>"The recommended duration of the comparative phase is <b>12 months</b>."</i></p> <p>Such a long duration of clinical trials will increase the likelihood of demonstration of a clinically relevant immunogenicity reaction. In fact, different manufacturing and expression techniques can have a clear influence on, e.g. the formation of aggregates and post-translational glycosylation which are known to have an effect on immunogenicity and the generation of neutralizing antibodies may significantly impair drug efficacy.</p>	<p>Approvals of new indications for innovator products were often based on short-term growth data, not on final height data. Since the intention of a 'biosimilar' somatropin is the demonstration of similar quality, efficacy and safety to a chosen reference product in order to achieve marketing authorisation for the established indications of the reference product (rather than obtaining new indications), an abbreviated clinical programme based on short-term growth of at least 6 months duration is acceptable.  The guidance document states that 12-month immunogenicity data are required (pre-authorisation). (NOTE: somatropin is a non-glycosylated protein)</p>
<b>Paragraph 5:</b>	<p>The draft Annex Guideline states <i>"Longer observation periods are particularly advisable if studies are performed in less sensitive models, e.g. in children with reduced growth potential due to advanced age or bone age"</i>.  We propose to rephrase the sentence to <i>"Longer observational periods are <b>requested</b> if study are performed in less sensitive models, e.g. in children with reduced growth potential due to <b>chromosomal, chronic somatic disease and other reasons for growth retardation</b>"</i>.</p> <p>Children without classical GHD may be regarded as "less sensitive model" e.g., Turner girls and SGA children. As final height data in such children had to be documented by the innovator Somatropin drugs it should be necessary for biosimilar products to show similar efficacy.</p>	<p>The annex has been modified to only give recommendations for the preferred model.</p> <p>See comment above</p>
<b>Paragraph 6:</b>	<p>As stated, some small changes in the formulation may result in an immune response affecting safety and efficacy. Furthermore, human studies conducted need to be of adequate size to be able to discount any unwanted effect such as local reactions, absorptions, etc. Therefore, it is important to ensure a risk assessment programme to evaluate the potential for immunogenicity effects of the similar biological medicinal product. Since the clinical importance of GH antibodies are influenced</p>	<p>A pharmacovigilance plan should be submitted in accordance with current legislation</p>
<b>5. Clinical Safety</b>		

	by the nature of the antibodies (being either binding or in worst case neutralising), this should be addressed.	
	Additionally, we noted that the applicant should provide comparative immunogenicity data of patients who participated in the efficacy trials for 12 months, therefore it is not clear to the members why the clinical efficacy section only asks for an observation period of a minimum of 6 months. Depending on the kind of host organism (yeast, bacterium or mammalian cell), a period of 1 year may need to be adjusted.	For proper assessment of growth at least 6-month data are required. The applicant is given the choice to define his primary efficacy endpoint for the 6-month or the 12-month time point. This may have implications for the sample size or the time point of application for marketing authorization. Nevertheless, 12-month immunogenicity data will be required pre-authorisation because anti-GH antibodies usually develop during the first 9 to 12 months of treatment.
<b>6. Pharmacovigilance plan</b>	A post-marketing surveillance programmes and pharmacovigilance commitments should be required for each indication.	A pharmacovigilance plan will have to be submitted in accordance with current legislation. The goal is to further assess the safety profile of the 'similar' product in a larger patient population including all approved indications.
<b>7. Extension of indication</b>	<p>The annex to guideline suggests that data from one patient population may be considered applicable for other patient populations. We consider that this is not possible for currently available growth hormone products, it is therefore important that this should not be possible also for biosimilar medicinal products.</p> <p>While the primary effect of somatropin in the childhood indications is height, several other claims of efficacy have been documented with the innovator somatropin drugs. The clinical data for each indication may not only reflect the content of somatropin per se in the drugs, but also the specific profile of split products which have been shown to have different affinity for the GH receptor. The clinical aim of GH treatment in e.g., Prader Willy Syndrome is not limited to height changes, but also changes in body composition. Likewise, the benefits of GH treatment in growth hormone deficient adults are not related to height changes, but to changes in body composition, muscle strength, bone mineral density etc. It is therefore necessary for biosimilar products to show similar efficacy of all claims of the innovator drug.</p> <p>This is also in line with Section 4 of Part II of Annex I to Directive 2001/83 where each indication for which similarity is claimed must be separately demonstrated in an appropriate comparative clinical trial.</p>	See comment above
<b>Introduction</b>	<p>Issues related to the characteristics and quality of the product (e.g. type of the cell line, production process, formulation, etc.) need also to be evaluated for the demonstration of similarity of medicinal products containing somatropin, as it is known that the development of neutralising antibodies is linked to product characteristics and the purity of the formulations. Such demonstrations should be performed during the development process of the similar biological medicinal product at the same time as the trials for safety and efficacy, in order to ensure clarity and consistency in the evaluation of these products. In particular, the Guideline should clearly state that the expression system used to produce another somatropin product is critical and may have a significant impact on its efficacy and safety. Therefore, the manufacturer of a somatropin product claimed to be similar to an already authorised one, should use as reference product a somatropin manufactured using the same expression system and vector.</p> <p>Amongst the somatropin products on the market, the first ones used the E-coli expression system, whilst another one was developed from a different expression system using murine expression cells. Hence, we expect that any new somatropin product developed with a different expression system and vector, should adhere to</p>	Generally agreed although the use of a different expression system per se would not preclude the assumption of 'biosimilarity'. (NOTE: somatropin is a non-glycosylated protein)

	<p>the precedent that has already been set. The rationale behind this is that every different expression system produces significantly different impurities both from the host cell line as well as the culture medium. The impact of foreign proteins to which the human population may not have been exposed previously is unknown and must be fully evaluated.</p>	
<p><b>Clinical studies</b></p>	<p>The Guideline should explicitly state that it only covers the recommendations for indications related to growth promotion in children.  The efficacy and safety in any indication can be impacted by the structural integrity of the active molecule and by the impurity profile of the product.</p> <p>a. Purity  The impurity profile of any recombinant product is determined by the host cell line used for the expression and production, the culture medium components, and the purification system employed.</p> <p>Structure  The structural integrity of recombinant medicinal peptide and protein products generated by prokaryotic and eukaryotic organisms is a major concern. Different expression systems (host cell as well as modifications of genetic constructs) and subsequent processes can lead to modifications such as amino acid sequence substitutions/mutations, post-translational modifications or conformational changes. A recent publication by Hepner et al entitled “Mass spectrometrical analysis of recombinant human growth hormone (Genotropin) reveals amino acid substitutions in 2% of the expressed protein” can serve as an example (Article published in Proteome Science 2005, 3:1 - attached as annex).  The above considerations impact both clinical efficacy and safety evaluations.</p> <p>Subsection 4.3 - Clinical efficacy studies  Paragraph 1  We suggest modifying the first sentence as follows:  “Human growth hormone receptors are differently distributed in various tissues and body organs. Therefore, equivalent therapeutic efficacy between the similar biological medicinal product and the reference product should be demonstrated for each indication in a direct comparison using the same posology and the same route of administration in at least one adequately powered, randomised, parallel group, confirmatory clinical trial.”(...)</p> <p>The justification for the insistence on one clinical trial per indication is based on the following two points:</p> <p>Receptors  Somatotropin has extensive and diverse metabolic effects based on activation and signal transduction of receptors differently distributed in various body tissues and organs. This is clinically reflected by the need to apply different treatment posologies on one hand, and evaluating the effects by different clinical endpoints in the different indications and patient populations on the other.</p> <p>Depending on the indication, growth hormone exerts its effect through interaction with the growth hormone receptor in different tissues such as growth-plate, muscle,</p>	<p>Part II, section 4 of the Annex I of Directive 2001/83/EC reads: “In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.” Therefore, extrapolation to other indications of the reference product is possible if appropriately justified.</p> <p>Since there is only one GH receptor and all actions of GH are thought to be mediated via this receptor, demonstration of similar efficacy and safety in a sensitive model (preferably in GH deficient children) may allow extrapolation to other indications of the reference product.</p> <p>Comparative 1-year immunogenicity data will be required based on the knowledge that anti-GH antibodies develop within the first 9 to 12 months of treatment. We are not aware that immunogenicity differs in the different approved indications. HIV and AIDS are not approved indications for GH treatment in the EU and are therefore not relevant.</p> <p>The issue of interchangeability of somatotropin-containing medicinal products is beyond the scope of this guideline</p>

	<p>liver, and adipocytes. Little is known thus far about the difference in growth hormone receptor binding kinetics and subsequent signalling changes in different tissues. Furthermore, it cannot be totally excluded that amino-acid substitutions and/or post-translational changes, such as alternate splicing products and aggregates, could influence growth hormone receptor binding and signalling in different tissues. For these reasons, it cannot be accepted that the efficacy and safety of somatropin in one indication can be extrapolated to another indication.</p> <p>Immunogenicity</p> <p>Immunogenicity is a potential risk associated with any injected protein. It is a multifactorial event that depends on the modifications of the structure, purity of the product as well as route of administration and patient population. It is well known that differences in manufacturing and in the final formulation, as well as post-translational changes such as aggregate formation, can increase the incidence of antibody formation.</p> <p>The risk of antibody development is not only determined by the physicochemical properties of the product and its impurities, but also by the condition of the patient's immune system. Since somatropin can be used in substantially different patient populations such as children and adults with or without growth hormone deficiency, and adults with HIV infection, one cannot claim that just one of these populations would be representative for all populations as far as immunological responses are concerned. Therefore, it is necessary to perform clinical trials that assess immunogenicity, safety and efficacy in each of these populations. The issue is particularly important in children where the potential development of neutralising antibodies with cross-reactivity to endogenous growth hormone may not only abolish treatment efficacy with any other growth hormone preparation, but could also deteriorate the primary growth disorder.</p>	
<b>Paragraph 5</b>	We recommend that the duration requirements of the comparative studies for a new somatropin product should not be less than the requirements fulfilled by the innovator company. Furthermore, related to the immunogenicity problem, long-term studies have to be considered	Approvals of new indications for innovator products were often based on short-term growth data, not on final height data. Since the intention of a 'biosimilar' somatropin is the demonstration of similar quality, efficacy and safety to a chosen reference product in order to achieve marketing authorisation for the established indications of the reference product (rather than obtaining new indications), an abbreviated clinical programme based on short-term growth of at least 6 months duration is acceptable. The guidance document states that 12-month immunogenicity data are required (pre-authorisation).
<b>5. Clinical safety</b>	We recommend that the second sentence in Section 5 be modified as follows: "The applicant should provide comparative immunogenicity data <b>on patients who participated in clinical trials of adequate size and during the entire trial period (minimum 12 months) with analyses performed at three month intervals</b> , using validated assays of adequate specificity and sensitivity".	No, but we agree that some modification of the wording would be helpful.
<b>Pharmacovigilance plan</b>	We suggest that the post-marketing surveillance programme mentioned in the Draft be requested for each indication.	A pharmacovigilance plan will have to be submitted according to legislation. The goal is to further assess the safety profile of the 'similar' product in a larger patient population including all approved indications
<b>Introduction</b>	We are somewhat unclear as to the requirements for analytical characterization of biosimilar Somatropin. The document appears to be lacking in any CMC related guidance. Does the guidance take for granted that the applicant has met CMC criteria already and if so where are those requirements documented? Should we	Quality issues will be addressed in a separate guideline. The current view is that product-class-specific guidance for quality is not needed. The demonstration of physico-chemical and biological comparability should be demonstrated according to state of the art methods

	<p>assume that the product has to meet only the European pharmacopoeia monograph standards?</p> <p>Further clarification should be provided on how stability of the similar product should be considered in terms of its impact on clinical outcome. Since the levels of degradation products can vary widely depending on impurities and formulation components/conditions, clinical safety and efficacy should be confirmed with the similar product at the end of its intended shelf-life</p>	
	<p>The guidance does not describe which product(s) should be used as comparator product(s). Since the formulations, pharmacokinetics, dosages and reported efficacy among existing Somatropin products can vary greatly which product should be used as a comparator product in all preclinical and clinical testing?</p>	<p>There is no requirement to use a specific reference product. The reference product must be authorized in the EU and the same reference product should be used for all aspects of the comparability exercise</p>
	<p>Section 3, last line: Add “currently approved” before “therapeutic indications of rhGHs”.</p>	<p>Agreed</p>
<b>4.3 Clinical studies</b>	<p>In general, recommendations for treatment of adults should be discussed in the guideline.</p>	<p>No, the guidance document only focuses on the description of the study design in the preferred model</p>
	<p>Page 4: <i>Longer observation periods are particularly advisable if studies are performed in less sensitive models, e.g. in children with reduced growth potential due to advanced age or bone age.</i></p> <p>We propose to rephrase the sentence to ‘Longer observational period is <b>requested</b> if study are performed in less sensitive models, e.g. in children with reduced growth potential <b>due to chromosomal, chronic somatic disease and other reasons for growth retardation</b>’. Children without classical GHD may be regarded as “less sensitive model” e.g. Turner girls and SGA children. As final height data in such children had to be documented by the innovator somatropin drugs it should be necessary for biosimilar products to show similar efficacy of the claims.</p>	<p>The annex has been modified to only give recommendations for the preferred model.</p>
<b>5. Clinical Safety</b>	<p>Since the clinical importance of GH antibodies are influenced by the nature of the antibodies (being either binding or in worst case neutralising) should be addressed.</p>	<p>Agreed. Both aspects are addressed in the general guideline</p>
	<p>The specificity and sensitivity of the immunogenicity test must be proven valid for the purpose as described in "Recommendations for the Design and Optimization of Immunoassays used in the Detection of Host Antibodies against Biotechnology Products" By: Anthony R. Mire-Sluis et al J. Immunol. Methods 2004. Likewise, the samples to be analysed for presence of antibodies must be obtained at time points with minimal interference of circulating drug.</p>	<p>It is self evident that the specificity and sensitivity of the immunogenicity test(s) must be proven valid for the intended purpose. This is part of the assessment of an application. Possible interference with antigen should always be taken into account. These issues are not specific to somatropin and are therefore addressed in the general guideline (i.e. <i>Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues</i>)</p>
<b>Introduction</b>	<p>The Agency has included the statement “The same receptors are thought to be involved in all therapeutic indications of rhGHs”. In is important to note that GH action is far more complex than can be explained on the basis of a single molecule-receptor interaction.</p>	<p>Although GH action most likely is complex and not yet fully understood, the same GH receptor appears to be involved in all currently approved therapeutic indications, which include growth promotion and normalization/improvement of body composition. Of course we cannot make assumptions about possible future indications.</p>
<b>2.Scope</b>	<p>The agency has established an important precedent in regards to its evaluation and regulatory approval of the various rhGH products currently available on the market. These rhGHs have been regarded by the Agency as separate and distinct molecular entities as determined by their distinct methods of production and different labels, indications, interactions, precautions, contraindications, warnings and dosages. As such, rhGH cannot be regarded as a drug “class” because the very concept of ‘bioequivalency’ for these various rhGH products does not exist.</p> <p>Each approved rhGH product is a well-characterized molecular entity for which a large body of analytical and process knowledge exists with each manufacturer.</p>	<p>The agency does not consider all sompatropin-containing medicinal products to be the same. Therefore, a single reference product has to be chosen for the whole comparability exercise and the SPC of the “biosimilar” medicinal product will largely be in line with the SPC of the reference product.</p>

	Bioequivalency between lots of a specific rhGH product is established based on this knowledge, and each company uses the same database to support process improvements. Note that one company's knowledge of its rhGH product would not be useful in evaluating the comparability of products resulting from a process improvement introduced into the production of another rhGH. This emphasizes the distinct nature of each rhGH product and the inapplicability of the drug "class" concept.	
<b>3.Non-clinical studies</b>	The Agency has recommended: "[non-clinical] studies should be comparative in nature and should be designed to detect differences in the response to the similar biological medicinal product and the reference medicinal product and should not just assess the response <i>per se</i> ". However, it is not apparent from the draft guidance document what parameters/criteria the Agency will accept for demonstrating equivalency when evaluating results from non-clinical studies of the similar biological medicinal product and the "reference medicinal product". Again, the Agency should provide an outline of its plans for recommendations regarding the demonstration of equivalence and provide the opportunity for further review and comment on their recommendations.	The proposed non-clinical studies are part of the overall comparability exercise. Since a variety of different parameters are evaluated in the non-clinical pharmacological and toxicological studies, a general recommendation regarding the demonstration of comparability between new rhGH and reference medicinal product (RMP) is not feasible. For the interpretation of <i>in vivo</i> pharmacodynamic studies (weight gain assay and tibia growth assay in immature hypophysectomized rats), reference may be made to "older" versions of the Ph. Eur., which specify acceptance ranges for the observed pharmacological effects in comparison with a defined hGH standard. In the case of non-clinical toxicity studies, the occurrence of "unexpected toxicity" (i.e. toxic effects only observed for the new rhGH, but not for the RMP) would certainly raise serious concerns about the comparability of the two products. In the case of quantitative differences in toxic effects observed for both new rhGH and RMP, assessment of comparability on a case-by-case basis appears warranted.
	The Agency has recommended that toxicological studies be performed, including local tolerance testing by repeat dose toxicity studies. However, toxicology studies should be performed in at least two different animal species (one in rodent and the other in non-rodent species) and be of 4 weeks to a maximum duration of six months for evaluation and detection of the longer-term effects of the similar biological medicinal product.	Assuming "analytical" comparability of new rhGH and reference medicinal product (RMP) and taking into account data published concerning non-clinical toxicity of hGH, a reduced non-clinical toxicological program (one 4 week, repeat dose toxicity study; local tolerance study, if feasible, as part of the repeat dose toxicity study) has been proposed, additional toxicological studies are not routine requirements. As it stands, this program is designed to provide: (i) information, as part of the overall comparability exercise, whether the non-clinical toxicological properties of new rhGH and RMP are comparable (ii) assurance that no "unexpected toxicity" (e.g. toxic effects induced by process-related impurities) will occur after application of the new rhGH to humans. The proposed non-clinical toxicological program is considered suitable to provide the required information. A supplementary repeat dose toxicity study in a second species and an extension of study duration up to 6 months are not expected to provide significant additional information (e.g. in the latter case, extensive formation of antibodies directed against the rhGH as a "foreign" protein would complicate/invalid study interpretation).
<b>4.3 Clinical efficacy studies and clinical safety</b>	The Agency has alluded to the fact that the response to rhGH is variable and dependent on the selected patient population, with GH-deficient children showing higher sensitivity to the effects of somatotropin in comparison to non-growth hormone deficient children who are treated with rhGH. In view of the differences in the clinical presentation, clinical response and the adverse effect profile of the various patient populations for which the rhGH products are currently prescribed, clinical efficacy studies should be carried out only within defined patient populations, rather than in a heterogeneous patient mix, so that a more appropriate and accurate interpretation of the primary outcome data can be obtained.	The guidance document states that GH-deficient, treatment-naïve, pre-pubertal children are the preferred model to be studied. This represents a homogeneous population.
	<u>4.3 Clinical efficacy studies and clinical safety</u> Further the Agency should provide guidance regarding acceptable equivalency	The acceptable equivalence margin depends on the chosen endpoint. More experience will be needed before clear recommendations can be made in the guidance document. For

	<p>margins for outcome data for these different and distinct patient groups. For example, for children with GH deficiency, an acceptable margin of equivalence might be defined by a difference in height velocity at 12 and 24 months of no more than +/- 1 or 2 cm/yr compared to the "reference medicinal product" if needed.</p>	<p>the time being, the applicant will need to justify the chosen equivalence margin based on a review of the data obtained with the reference product and, if applicable, with other somatropin containing medicinal products.</p>
<p><b><u>Pharmacovigilance plan</u></b></p>	<p>The sponsors of biosimilar MAA should be required to create, maintain and analyse post marketing surveillance database for a period of no less than 5 years as a post approval commitment. This requirement should be part of scientific advice during development of the biosimilar as well as a post-approval requirement.</p>	<p>The exact post-marketing requirements will depend on a review of the data submitted with the application for marketing authorization. Scientific advice is recommended but cannot be enforced.</p>
	<p>Under no circumstances should the Agency allow the use of new GH preparations with injection devices that are currently available unless their use has been properly evaluated and approved as safe and effective by the Agency.</p>	<p>Medical devices are not approved by CHMP.</p>

These comments and the identity of the senders will be published on the EMEA website unless a specific justified objection was received by EMEA.