17 January 2011

EMA/38050/2011

Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (EMEA/CHMP/BMWP/301636/2008)

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

Stakeholder no.	Name of organisation or individual
1	**EBE (European Biopharmaceutical Enterprises)**
2	**EGA-EBG (European Biopharmaceuticals Group-European Generic medicines Association)**
3	**Universidad Autónoma de Barcelona – Dept. of Pharmacology**
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1. GENERAL COMMENTS

Stakeholder No.	General Comment (if any)	Outcome (if applicable)
1	The proposed guideline on the non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins is well written and provides reasonable guidance on the appropriate evaluation of biosimilar erythropoietins.	Comment is appreciated.
1	The intention to refine and adapt the guideline to the experience gained is to be welcomed. However, recent events (i.e., termination of a pivotal clinical study with an epoetin-alfa biosimilar due to one case of PRCA and one case of neutralizing antibody formation) demonstrate that lowering the requirements, particularly concerning safety, should be undertaken with caution. It would therefore appear advisable to postpone any decrease in safety requirements until adequate experience has been obtained with the marketed epoetin biosimilars. As stated also under section 2 only two biosimilar epoetin products have been approved, neither for sc use in renal anaemia and both have been marketed only for a short period of time.	Requirements are not lowered with regard to the most important safety issue, i.e. immunogenicity since amount of pre-marketing SC data in renal anaemia patients will not be reduced. In addition, prelicensing data are expected to reveal excessive immunogenicity only. The real frequency of PRCA, usually a very rare event, can only be properly assessed post-marketing. Submission of an appropriate PhV plan is obligatory for every NDA including biosimilars.
1	Editorial comment: A clearer differentiation and use of the terms "erythropoietin", "recombinant erythropoietin" and "epoetin" would be desirable from the user's point of view. We would recommend the use of "erythropoietin" for the natural hormone and "epoetin" for the recombinant versions of it as suggested in line 47 of the draft guideline.	Taken into account

2. SPECIFIC COMMENTS ON TEXT

Line No of the first line(s) affected	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
	3	**Comments:** You will find below a suggestion which is based on the following evidence-rationale: 1. Many countries have issued specific legislation on interchangeability of biotech-derived pharmaceuticals, It certainly is a matter of concern. Quite a bit of them currently do not allow such automated substitution (unlike what happens with generics) 2. Such "rule" seems reasonable in the light of the uncertainty of the biological behaviour of such novel therapeutic proteins. In particular with respect to safety considerations. 3. However, health professionals and national authorities do often argue whether such measure is indeed reasonable. In other words, they claim that if, for instance biosimilarity of two products has been demonstrated by all means, interchanging both products for economic reasons should not be a matter of concern. 4. Yet interesting and well taken, inderect evidence shows that this is not fully correct at least at the saftey level. As an example from a past experience, despite endogeneous erythropoietin is tolerated by the immune system (is non immunogenic), when confronted to an exogeneous recombinant EPO, the endogeneous counterpart may convert into an immunogenic protein (immunological tolerance is therefore broken). 5. This indicates that an otherwise non-immunogenic molecule, can switch to immunogenic under the appropriate "stimulating" conditions. 6. There is therefore concern that, for mostly unknown reasons, a protein that has been demonstrated under the EMEA guidelines not to be immunogenic or to be hardly immunogenic, can turn into an immunogenic one if given to a patient that has previously been exposed to one or several similar products. 7. This justifies the concern that making biotech proteins interchangeable could have at some point an impact on the immunologic tolerance to one of the molecules. It therefore explains the fact that national legislation is	Decision on automatic substitution is not within the remit of the CHMP/EMA but a national issue. However, EMA has issued a statement that "biosimilar and biological reference medicines are similar but not identical" and that "the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional." Available from: URL:http://www.ema.europa.eu/pdfs/human/phvwp/81624809en.pdf

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		cautious when deciding upon interchangeability of biotech products. 8. In my view, until this very confusing area is scientifically clarified, interchangeability should not be allowed. 9. Again, in my opinion EMEA needs to address this in a general basis, since sponsors might need to include such variable into their biosimilars development plans. **Proposed changes:** All the rationale above could be summarized in a paragraph such as the following: "Despite biosimilarity is finally demonstrated for a therapeutic recombinat protein, i.e. similar quality, efficacy and safety are shown under a comparability exercise, sponsors need to be aware that automatic therapeutic substitution of both products will not be authorised. Through indirect evidence, biomedical experience shows that safe molecules can switch to unsafe when exposed to similar products, e.g. endogeneous proteins shift from non-immunogenic to immunogenic when exposed to similar exogenous agents. In order to minimize the potential risks associated with the exchange of the innovator-reference product by a biosimilar therapeutic protein, only if such substitution is extensively and specifically addressed under relevant clinical studies, the product would be awarded such capability within the approval process. Consultations with EMEA are recommended before undertaking research aimed at addressing the interchangeability" It is my suggestion that EMEA starts including such statements in the new Erythropoietin guideline and then progressively transcribes it to other relevant papers to be issued or updated in the coming future. Such decision has certainly economical implications and it would help companies decide upon the convenience of developing an EPO biosimilar (for instance) that ultimately will not be allowed to being interchanged therapeutically with alternative EPOs.	
Line 16	**2**	As this guideline presents the requirements for demonstration of comparability of two recombinant human erythropoietin containing medicinal products this should also be stated in the keyword section.	Included

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		Please add the word: comparability	
Line 27:	**1**	**Comments:** We assume "erythropoietin" stands here for recombinant human erythropoietin, the latter is, from our perspective, similar with the term "epoetin"?	Taken into account
Line 36:	**1**	**Comments:** See comment above. It maybe useful to clarify here that human recombinant erythropoietin is later also referred to as "epoetin" (see line 37, first word)	Taken into account
Line 39	**2**	Immunogenicity is included in safety and does not need to be pulled out for special consideration as it is unclear what role glycosylation differences play in the development of immune responses. We suggest either removing the words: particularly immunogenicity or replacing the word "particularly" by "including"	The wording has been changed to "safety including immunogenicity".
Line 56	**1**	**Comments:** The statement should be broadened to include other immunogenicity events than PRCA. See also next comment. **Proposed change (if any):** Because antibody-induced PRCA ***and more generally immunogenicity events*** ~~is a~~ ***are*** very rare event***s*** and usually takes months to years of epoetin treatment to develop, such events are unlikely to be identified in pre-authorisation studies. In addition, possible angiogenic and tumour promoting effects of epoetin might be of importance in selected populations.	Not taken into account. So far, the only clinically relevant immunogenicity event related to epoetins is PRCA.
Line 87	**2**	It is stated that erythrogenic effects should be compared in an appropriate animal assay. As an example of suitable assays reference is made to the European Pharmacopoeia. However, the EMEA guideline and the monograph have been developed further independently from each other. In the current draft of the monograph revisions were made to the bioassay section, i.e. the polycythaemic mouse is deleted and a cell based assay will be added as an alternative. Such (potential) revisions should be taken into account. Please remove the sentence in the brackets: ~~(e.g. the European Pharmacopeia polycythaemic and/or normocythaemic mouse~~	The wording of the revised guideline has been modified to take into account the (potential) revision of the European Pharmacopoiea. However, reference to the normocythaemic mouse assay has been kept, since this assay is retained in the draft version of the erythropoietin monograph as one of the methods suitable for characterization of erythropoietin activity.

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		~~assay; data may be already available from quality-related bioassays)~~	
Paragraph 3 ("Discussion")	**4**	In its current version, the guideline suggests that a correction study in a pre-dialysis population would be useful to demonstrate biosimilarity of an epoetin product. We would like to stress that from a practical point of view, organising such a study in the EU today appears almost impossible for a biosimilar epoetin alfa since: ▪ It is specified that the reference product, Eprex / Erypo, should be used according to its accepted indications only, namely: ▪ In a pre-dialysis population, Eprex / Erypo can be prescribed to <u>severe</u> anaemia patients only, however: ▪ Such patients would be in principle almost impossible to recruit in the EU: it would be in contradiction with the European Best Practice Guidelines not to treat CKD patients before they reach a severe anaemia state. We therefore would like to suggest that one phase III study in a haemodialysis population should be sufficient to demonstrate biosimilarity of an epoetin product. As suggested by the concept paper, the issue of the extrapolation of one route of administration to the other route of administration would be treated separately via appropriate bridging studies.	The revised guideline now describes different options for demonstrating similar efficacy. It is nowhere stated that only patients with severe anaemia can be included in the clinical trials. Adhering to recommendations from European Best Practice Guidelines is fully acceptable.
Paragraph 3 ("Discussion")	**4**	We would like to propose that the phase III trials for a biosimilar product does not need to include a comparator group of patients treated with the reference product, provided a full quality dossier for the new product is presented, and that the animal and phase I PK/PD studies have demonstrated an equivalent behaviour of the biosimilar product with the reference product. Our rationale is to concentrate the resources on the collection of valuable clinical information for the new, biosimilar product instead of spending part of these resources for adding even more data to the already existing extensive information on the marketed reference product. In our opinion the principal interest must be the detailed knowledge of efficacy, reliability, safety and lack of immunogenicity of the product under development.	Disagreed. Comparison of efficacy and safety (including immunogenicity) in at least one indication is necessary and an essential element of the comparability exercise and, thus, of the biosimilarity concept.

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		The efficacy (dosage & response), safety and immunogenicity information generated for the new, biosimilar product during the phase III trials should be compared to the wealth of already existing and published phase III and phase IV clinical trial data concerning the reference product.	
Line 56 and Line 215	**1**	**Comments:** "*Because antibody-induced PRCA is a very rare event and usually takes months to years of epoetin treatment to develop, such events are unlikely to be identified in pre-authorisation studies*" // "*Due to their rarity, neutralising antibodies or even PRCA are unlikely to be captured pre-marketing*": it is now clear that PRCA cases may even occur within the limited patient numbers studied pre-authorisation. http://www.bfarm.de/cln_012/nn_421158/DE/Pharmakovigilanz/risikoinfo/epo.html__nnn=true In order to avoid approval of biosimilar products with increased PRCA risk, it should also be stressed that pre-approval immunogenicity studies with science based study designs are necessary, even if the PRCA risk will have to be monitored post-approval. We suggest modifying the text line 57 to: **Proposed change (if any):** **Line 56** "~~Because~~ Antibody-induced PRCA ***and more generally immunogenicity events*** ~~is a~~ ***are*** very rare event***s*** and usually takes months to years of epoetin treatment to develop. ~~such events are unlikely to be identified in pre-authorisation studies~~ ***Nevertheless, such events have been identified in pre-authorisation studies***". **Line 215** " ~~Due to~~ ***Despite*** their rarity, neutralising antibodies ~~or~~ ***and*** even PRCA ~~are unlikely to be~~ ***have been*** captured pre-marketing […]"	Guideline text has been modified. However, a more general wording is preferred.
Line 109 and	**1**	**Comments:** As elsewhere in the document proposed studies are clarified to be renal only, it may be considered worthwhile to refer to the type of clinical studies expected in	The current place for description of the study population is considered appropriate.

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Line 126		an early part of this section too.	
Line 112 and Line 195	**1**	**Comments:** The proposed revised version of the guideline considers a scenario when an applicant seeks approval for only one route of administration (IV or SC), and describes simplified clinical studies for this case. Regardless of whether this is a realistic scenario, it has to be demonstrated in clinical practise that epoetin biosimilars which have been developed and approved for one route of administration only will not be used for both pre-dialysis and dialysis patients, and not using both application routes. This may be associated with an increased safety risk if e.g. a product licensed (and clinically tested) only for IV use is given subcutaneously which may lead to higher immunogenicity.	The aim of the clinical development of a biosimilar is to compare test and reference in a "sensitive test model", able to detect potential differences between products. For extrapolation of efficacy data from SC route to IV route or vice versa bridging data are necessary. Whereas SC immunogenicitiy data can be extrapolated to IV use, the opposite scenario is not possible. This is clearly stated in the guideline. If only one route of administration is licensed for a biosimilar, this will be clearly stated in the product information.
Line 125	**1**	**Comments:** There is a possible typographical error here. We would propose the following minor amendment: **Proposed change (if any):** 'and therefore no**t *a*** suitable endpoint in clinical trials'	Has been corrected.
Lines 130 - 132	**1**	**Comments:** Due to the differences in bioavailability between the routes of administration we do not consider it sufficient to perform a clinical trial for one route and provide bridging data for the other route of administration (e.g. IV to SC and vice versa). Separate clinical trials for each route of application applied for are needed to support respective labelling. Especially for SC application, long-term safety data, including assessment for formation of anti-EPO-antibodies, are deemed necessary to minimise the risk for PRCA with any new epoetin product.	See above response.
Line 143	**2**	It should not be essential to carry out both a correction and a maintenance study. Assuming demonstration of PK/PD similarity, the efficacy and safety of a product can be adequately demonstrated in either a maintenance or a correction study. **Extrapolation in terms of efficacy either from IV to SC or from SC to IV should be possible, however it is noted that extrapolation in terms of**	The revised guideline provides two options, either performing two separate clinical trials for SC and IV use (the only option proposed in the previous guideline) or performing one clinical trial and bridging via PD/PD data (the newly introduced option based on experience with

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		safety from IV to SC is not appropriate. Please reword the sentence to read : For demonstration of similar efficacy, it is recommended to perform a study using epoetin in either a renal pre-dialysis or renal haemodialysis population. Extrapolation in terms of efficacy to the iv or sc route would be possible if demonstration of similarity has been shown through acceptable PK/PD studies.	marketing authorisation applications). Performing two separate clinical trials certainly represents the ideal scenario. It is however clear from the new wording that this is not mandatory. The following sentences have been included for clarification: "The following sections present different options and recommendations on how to demonstrate similar efficacy of two epoetin-containing medicinal products. A sponsor may choose from these options or modify them but should always provide sound scientific justification for the approach taken."
Line 147	**2**	Assuming similarity in PK/PD, dynamics and dosing could be equally well be demonstrated in either correction or maintenance phases. It should not be a requirement to complete both a maintenance and a correction study. Furthermore the comment about characterization of the safety and immunogenicity profile is correct only for the sc route of administration but is independent of whether the study is correction or maintenance. Please remove the complete sentence : A correction phase study will determine response dynamics and dosing during the anaemia correction phase and is particularly suitable to characterize the safety and immunogenicity profile of the similar biological medicinal product.	The sentence in question has been modified as follows A correction phase study will determine response dynamics and dosing during the anaemia correction phase and is particularly suitable to characterize the safety ~~and immunogenicity~~ profile related to pharmacodynamics of the similar biological medicinal product.
Line 147	**1**	**Comments:** The correction phase is not appropriate to assess rare immunogenicity event like PRCA. **Proposed change (if any):** A correction phase study will determine response dynamics and dosing during the anaemia correction phase and ***contribute*** ~~is particularly suitable~~ to the characterisation of the safety and ***high- level*** immunogenicity profile of the similar biological medicinal product.	Immunogenicity has been deleted due to possible misunderstanding.

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Line 148	**2**	Side effects resulting from the immunogenicity profile of an ESA are very rare and can hardly be detected in a phase 3 trial of a suitable size and length. Thus a correction phase study should focus on response dynamics and dosing and in addition in particular on the safety of the patients. In case the sentence above is not removed, please reword the sentence as follows: .. is particularly suitable to characterize the safety ~~and immunogenicity~~ profile of the similar biological medicinal product. …	The sentence has been modified accordingly (see above response).
Line 149	**2**	Apart from the difficulty of finding ESA naive patients in order to complete an appropriately powered efficacy study, the study of such patients does not add any new information that could not be collected from ESA pre-treated patients. Please remove the complete sentence : It should only include treatment naïve patients or patients previously treated after a suitably long epoetin-free and transfusion-free period (e.g. 3 months).	We believe that a correction phase study is particularly suitable to characterize the safety profile related to pharmacodynamics of the similar biological medicinal product. A correction phase study only makes sense in a population with sufficiently low Hb considering that the lower limit of the Hb target range is 10 g/dL. Baseline Hb values should be largely devoid of confounding previous treatments including epoetins and RBC transfusions to reduce variability and because the primary endpoint measures the change from baseline. This makes a certain treatment-free period prior to randomization necessary.
Line 149	**1**	**Comments:** A 6 month epoetin free period is more appropriate if the objective of the correction phase is also to evaluate immunogenicity. **Proposed change (if any):** It should only include treatment naïve patients or previously treated patients after a suitably long epoetin-free and transfusion-free period ~~(e.g. 3 months)~~ ***of 6*** months.	Considering a normal erythrocyte half life of approximately 120 days, which is even shorter in patients on dialysis, a 3- month epoetin -and transfusion-free period is considered sufficient.
Line 151	**2**	A maintenance study should be recommended for efficacy comparability due to sensitivity to detect dose differences. A correction study should not be recommended or required. Please reword the sentence to read :	The guideline does not insist on specific studies being performed but gives recommendations and the considerations behind. The Applicant may choose from different options but should always justify the

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		A maintenance phase study in stable iv renal haemodialysis patients is recommended to demonstrate efficacy comparability. Such patients generally receive regular ESA administration and are sensitive to detect differences in biological activity between the similar and the reference product.	approach taken. (also see above response)
Line 156	**2**	For a maintenance phase trial the patients should be optimally titrated on the reference product. As patients can be included in the trial which are either already under treatment with the reference product or under treatment with a different marketed erythropoietin it is regarded necessary to have a run-in period of at least 3 months to ensure stabilized patients for randomisation. Please reword the bracket to read: (for at least 3 months)	Content of the brackets has been modified to read: (usually at least 3 months)
Line 156	**1**	**Comments:** We would suggest that 3 months is not long enough to document maintenance of a stable haemoglobin. We recommend at least 6 months (a standard follow up period as supported in the literature) observation time in the maintenance phase for long acting epoetins in which dosing intervals beyond Q2W are proposed. **Proposed change (if any):** The study design for a maintenance phase study should minimise baseline heterogeneity and carry over effects of previous treatments. Patients included in a maintenance phase study should be optimally titrated on the reference product (stable haemoglobin in the target range on stable epoetin dose and regimen without transfusions) for a suitable duration of time ~~(e.g. 3 months)~~ ***of 6*** months	The wording has been adapted for long-acting epoetins but without specifically stating the duration of the treatment-free phase because this will obviously depend on the pharmacodynamic characteristics of the specific product. Otherwise see above response.
Line 169	**2**	Making the epoetin dosage a co-primary endpoint has a significant impact on the sample size and also induces the difficulty of defining the corresponding equivalence limits for this endpoint. It is agreed that the epoetin dose should also be looked at closely in terms of biosimilarity of the products and its impact should be investigated in the context of the equivalence testing by, for e.g., including it as a covariate into the analysis model. Please reword the sentence to read: Therefore, epoetin dosage should be analysed in detail as a secondary endpoint. In particular, epoetin dosage could be considered to be included as a covariate	Achieving similar Hb (changes) with similar dosage(s) compared to the reference product is essential for a biosimilar epoetin. If the sample size is chosen too small, the results may not provide sufficient confidence that this goal can be achieved. In the light of reduced clinical trial requirements in the new version of the guideline, at least one sufficiently powered high-quality clinical trial can be expected.

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		in the model used to assess the equivalence of the primary endpoint.	
Line 170	**1**	**Comments:** In the previous version, a comparative phase of 6 months in the correction phase study as well as a follow-up for "at least three and ideally 6 months" in the maintenance study was required. It is not clear why the assessment should be shifted to 5 months minimum, we suggest keeping it to 6 months unless there is strong rationale for the proposed change? We would also suggest removing the possibility of performing the efficacy assessment earlier as it provides unclear clinical guidance. **Proposed change (if any):** The primary efficacy endpoints should preferably be assessed after ~~5 to~~ ***6*** months in both the correction phase as well as the maintenance phase study in order to avoid potential carry-over effects from baseline treatment and allow full assessment of potential differences in both endpoints in the presence of stabilised haemoglobin levels and epoetin dosages. ~~If the primary efficacy assessment is performed at an earlier time point the applicant will need to demonstrate that potential differences in efficacy have been fully captured.~~	In studies with biosimilar epoetins, a 4-week evaluation phase between month 5 and 6 has been found suitable. The wording has been revised to make this clearer.
Line 176	**2**	As the epoetin dosage should only be considered as a *secondary* endpoint, there are no co-primary endpoints for the equivalence assessment. Please reword the sentence to read: The equivalence margin of the respective primary endpoint should be pre-specified and appropriately justified…	Disagree. See above response.
Line 177	**1**	**Comments:** Some clarification would be useful here. Does the Agency prefer a comparison of mean/median haemoglobin between the study groups or rather a comparison of haemoglobin values between the groups using the area under the curve method? Or rather a comparison of the percentage of responders per study group? If the haemoglobin endpoint is specified in terms of mean change in haemoglobin, the equivalence margins are specified (+/- 0.5 g/dL). It is	We believe that it is clear from the units used that the recommendation does not refer to AUC values. So far, no experience has been gained with the Hb responder definition and only limited experience with epoetin dosage. Therefore, stating strict equivalence limits is not considered appropriate at the present time.

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		proposed that the Agency also specifies equivalence margins for other forms of the haemoglobin endpoint (e.g. haemoglobin responder rate, haemoglobin maintenance rate). It is also proposed that the Agency specifies an equivalence margin for the co-primary endpoint referred to as "Epoetin dosage". The Agency should also advise that the Epoetin dose endpoint will not usually be normally distributed, so methods of estimating any difference in Epoetin dosage will need to take this into account. **Proposed change (if any):** ~~If~~ ***When change in*** haemoglobin is used as primary endpoint, an equivalence margin of =/- 0.5 g/dL is recommended, ***When haemoglobin responder rate or haemoglobin maintenance rate is used, an equivalence margin of =/- 10% is recommended***. Transfusion requirements should be included as ~~an important~~ ***a*** secondary endpoint. ***When the weekly epoetin dosage is used as the epoetin dose co-primary endpoint, the recommended equivalence margin must not exceed +/- 15%. Methods for estimating differences between groups for this endpoint should account for the fact that this endpoint is not normally distributed.***	
Line 180	**2**	This approach should not be 'an alternative approach', rather the recommended approach. This would also minimise the number of patients required to be treated in phase III studies. Please reword the sentence to read : It is recommended that demonstration of comparable efficacy, for both iv and sc routes of administration, is shown in a single comparative sc clinical trial. Extrapolation of this efficacy data to other route of administration can be achieved through provision of comparative single dose and multiple dose PK/PD bridging data in an epoetin-sensitive population (e.g. healthy volunteers).	The wording has been slightly changed to indicate that both approaches are possible without clearly stating a preference.
Lines 180-183	**1**	**Comments:** As indicated in the comment for Lines 130-132 above, we do not believe that providing bridging data between the different routes is sufficient, especially if this data is solely based on studies in healthy volunteers.	From a scientific point of view bridging of efficacy data with multiple dose PK/PD data is considered acceptable. Healthy volunteers would present a "sensitive test model", able to detect potential PK and PD differences between products.

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Line 188	**2**	There is no rationale why comparative immunogenicity data should be generated in a correction study. Please remove wording : correction phase	Not clear what is meant. Line 188 does not contain such a statement. Reasoning for the general requirement of comparative immunogenicity data is provided in section 4.3 "Clinical Safety" of the guideline. See also comment below.
Line 190	**2**	As discussed above there is no rationale for requiring a correction study as opposed to a maintenance study Please remove wording : correction phase……as described above	The guideline does not insist on specific studies being performed but gives recommendations and the considerations behind. The Applicant may choose from different options but should always justify the approach taken (also see above comment).
Line 191	**2**	It is generally understood and accepted that immunogenicity risk cannot be adequately studied in phase III trials because of the relatively small number of patients included. As such it is inappropriate to extend the study beyond the time required to demonstrate efficacy and non-immunogenic safety comparability –3-6 months. Follow-up data should be submitted during or post review and the study of immunogenic risk should also be included within the risk management plan. Please reword the sentence to read : …test or reference for a total of 12- months to obtain 6-month comparative immunogenicity data (to be submitted with the initial application) and a follow-up of additional 6- month immunogenicity data (non-comparative, to be submitted during review or post-approval).	In the absence of standardized assays, concomitant immunogenicity data on the reference medicinal product are important for proper interpretation of results. Six-month comparative data may not be sufficient since it takes, on average, about 12 months for PRCA to develop (we don't know how long it takes for neutralising antibodies to develop). For comparative phases shorter than 12 months, the applicant will need to provide sound argument that this does not increase the uncertainty about the immunogenic potential of the biosimilar epoetin. In other words, the applicant may choose to go for a shorter comparative phase but takes a certain risk with this approach. In any case, overall 12-month immunogenicity data on the test product need to be provided pre-licensing.
Line 195	**1**	**Comments:** As described in Section 4.2. under "clinical efficacy studies", correction and	Experience with biosimilar epoetin applications indicated that differences, if present, can be

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		maintenance phase achieve different objectives. Both studies are clinically useful to demonstrate comparison in haemoglobin target, dosage and safety. **Proposed change (if any):** If only ***the Intra-Venous*** ~~one~~ route of administration is applied for, a single dose PK/PD study and ~~either~~ both a correction phase ~~or~~ ***and*** a maintenance phase study as described above should be performed.	found in both types of trials. Requesting two trials for one route of administration is considered excessive.
Line 198	**2**	As discussed above a maintenance study should be recommended for either iv or sc use. Please remove the complete sentence : Therefore, a correction phase study may be most appropriate in case of intended SC use and a maintenance phase study for IV use.	As stated above, there are no strict requirements for certain studies (in fact, there is flexibility). To make this clearer, the following sentences have been included: "The following sections present different options and recommendations on how to demonstrate similar efficacy of two epoetin-containing medicinal products. A sponsor may choose from these options or modify them but should always provide sound scientific justification for the approach taken".
Line 201	**1**	**Comments:** **"***Comparative safety data from the efficacy trials are usually sufficient to provide an adequate pre-marketing safety database*" We would recommend to state here that the adequacy of the pre-approval safety database should be scientifically justified.	Experience with biosimilar applications indicate that the number of patients required for adequate efficacy studies with acceptable equivalence margins is appropriate to characterise the safety profile of the biosimilar epoetin.
Line 203	**1**	**Comments:** The section (and line 53) appropriately highlights that there are other events of interest in addition to PRCA, but places most emphasis on this. It is proposed that additional attention should be placed on screening for venous thrombosis and hypertension. We would suggest adding tumour progression to the list of adverse events of specific interest. **Proposed change (if any):** Adverse events of specific interest include hypertension/aggravation of hypertension and thromboembolic events ***and tumour progression. Patients***	The tumour-promoting potential of epoetins is considered a class-effect. Since pre-licensing studies are limited and proposed to be performed in patients with renal anaemia such effects cannot be studied pre-licensing. This issue should, however, be addressed in the RMP plan. Tumour-promoting potential has been included in section 4.4 Pharmacovigilance Plan.

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		<u>should monitored for these adverse events throughout the clinical investigation of the erythropoietin.</u>	
Line 204	**2**	As discussed above the recommended duration of the phase III study should be 6 months. A 12-month comparative study is unnecessary and is unlikely to add any significant new information. Therefore 6-month comparative immunogenicity data at the time of submission should be sufficient, however a further 6-months non-comparative follow-up could be submitted at a later time during or post review/approval. Please remove the complete sentence or change the sentence to read: The applicant should submit 6-month comparative immunogenicity data pre-authorisation with additional 6-month follow-up immunogenicity data for the biosimilar erythropoietin product during review or post-authorisation.	Disagree. See above response.
Line 204	**1**	**Comments:** We would suggest that the use of the term "Preferably" does not seem adequate considering the outcome of Hexal S.C. trials. This immunogenicity trial is pivotal in the assessment of biosimilarity. **Proposed change (if any):** The applicant should submit ~~preferably~~ 12-month comparative immunogenicity data pre-authorisation.	Has been taken into account.
Line 208	**1**	**Comments:** We would suggest that in view of the outcome of the Hexal S.C. trial it seems risky to allow any deviation to a 12 month immunogenicity study and would recommend to delete the corresponding statement. **Proposed change (if any):** ~~If the comparative phase of the immunogenicity assessment is less than 12 months the applicant will need to provide sound argument that this does not increase the uncertainty about the immunogenic potential of the biosimilar epoetin.~~	The reduced period refers only to the comparative phase, not to the requirement of overall 12-month immunogenicity data. The paragraph has been rephrased for clarification.
Line 211	**2**	It is stated that the antibody assay should be able to detect both early and late immune responses. The aspect of early immune response is related to the detection of IgM. However, IgM antibodies have no relevance for the patient's safety as to date	Disagreed. Especially with epoetins, immune responses should be captured as early as possible and the concerned patients should be closely followed.

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		only IgG-class anti-Epo antibodies have been shown to be neutralizing and to be able to induce a PRCA. When IgM antibodies have been detected, they have been found in treated patients but also in naïve patients who never received EPO. These antibodies were of low affinity, were not detected by RIP and by bioassays, none of the patients developed PRCA or any significant treatment related pathology (Thorpe R. and Swanson SJ. (2005) and Swanson S. (2004)). Please reword the sentence to read: The use of a validated, highly sensitive antibody assay, able to detect late immune responses, is mandatory.	
Line 211	**1**	**Comments:** The text infers the need to discriminate between high and low affinity antibodies by reference to the early and late immune responses, but it is considered worth emphasising this in more detail due to the importance of this analysis to patient safety. **Proposed change (if any):** The use of a validated, highly sensitive antibody assay**(s),** able to detect both early ***(low affinity antibodies, especially IgM class)*** and late ***(high affinity antibodies)*** immune responses, is mandatory.	Taken into account.
Line 221	**1**	"*the immunogenicity database should include a sufficient number of SC treated patients with renal anaemia, unless SC use in this population is not applied for*": **Comments:** This statement allows for immunogenicity assessment in IV treated renal anemia patients only if SC treatment in anemia is not applied for. The text does not indicate whether the immunogenicity database should include SC treated patients if the application includes use of the epoetin biosimilar in oncology indications (with SC application), at higher dose. Due to the important, and potential serious consequences, of epoetin immunogenicity, we recommend that the safety database always includes a minimum number of SC treated patients for assessment of risk which may not be possible with IV treated patients alone.	The current wording is preferred. A sufficient number is usually higher than a minimum number. Up to now, no cases of PRCA have been reported in immunocompromised cancer-patients. Therefore, the availability of SC immunogenicity data for approval of the oncology indication is not considered necessary. If SC use in renal anaemia patients is not applied for (which will likely not be the case after reinstatement of the SC route for epoetin alfa), no SC immunogenicity data can be

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		We also recommend that this section is revised to make the expectations on immunogenicity studies clear. **Proposed change (if any):** Since the SC route of administration is usually more immunogenic than the IV route and patients with renal anaemia constitute the population at risk for developing anti-epoetin antibody induced PRCA, the immunogenicity database should include a ~~sufficient number~~ ***minimum number*** of SC treated patients with renal anaemia, unless SC use in this population is not applied for.	requested in this population. In such cases, a clear warning regarding SC use will be included in the product information.
Line 223	**1**	**Comments: Pharmacovigilance Plan** Since it is inferred that studies in renal anaemia will allow extrapolation to use in chemotherapy induced anaemia, where it is acknowledged (Line 45) that considerable higher doses are required, it is proposed that there should be some acknowledgement in this section that careful pharmacovigilance may be required during initial use of these products at this significantly higher dose, where there will be little safety experience at time of initial approval. **Proposed change (if any):** Within the authorisation procedure the applicant should present a risk management programme/pharmacovigilance plan in accordance with current EU legislation and pharmacovigilance guidelines. ***Special attention should be given to measures to assess indications not previously studied (for example if only renal anemia studies have been completed at time of authorisation, where dose exposures are lower than with treatment in chemotherapy induced anemia)*** The risk management plan should particularly focus on rare serious adverse events such as immune mediated PRCA.	Since the proposed studies in renal anaemia patients (and healthy volunteers) are sensitive to detect potential differences in bioactivity, extrapolation of efficacy data to a rather insensitive oncology population is considered possible without further data. A risk management plan has to be submitted with any new MAA including biosimilars. This RMP is subject to discussion and approval by CHMP. No need to specifically state the proposed text in the guideline.
Line 227	**2**	The requirements concerning the risk management plan should be summarised and the sentence reworded to also reflect the comments in Lines 191 and 204 appropriately. Please reword the sentence to read: In order to further study the safety profile of the similar biological medicinal product, particularly rare serious adverse events such as immune medicated	The Applicant will have to submit a RMP at the time of marketing authorisation application. This will be evaluated by CHMP and modified if necessary (based on safety concerns related to the substance class, the reference product and/or the product applied for). Flexibility is needed as regards the best approach for a

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		PRCA, safety data should be collected from a cohort of patients in an appropriate PASS representing all approved therapeutic indications.	specific safety issue. Therefore, no specific requirements should be mentioned in the guideline.
Line 224-227	**1**	**Comments:** Pharmacovigilance: the text is limited to the request for a risk management plan/pharmacovigilance plan in accordance with current EU legislation. Given the fact that recent experience has shown that there may be a risk connected with SC use of epoetin biosimilars, special active pharmacovigilance activities should be required. Furthermore, practical experience has shown that confusion arose due to the use of different INNs for epoetin biosimilars, which however relate to the same reference product. This makes also pharmacovigilance and traceability more difficult. In accordance with WHO INN Working Document 08.242, regulators are responsible for checking and validating if an INN is correctly used and corresponds to the substance that is the subject of the Marketing Authorization. In order to ensure traceability of the epoetin product given to patients in case of safety-relevant events, the guideline should clarify that manufacturers have to apply for a distinct INN unless differences in glycosylation vs. the reference product are excluded/disproven. **Proposed change (if any):** Add the following paragraph: "***Applicants and Regulatory Authorities should ensure that all epoetin products are appropriately identifiable following WHO naming conventions that allow clinical relevant differences (glycosylation / differences in routes of administration or indications approved/ differences in safety profile) to be identified by doctors and facilitate appropriate traceability***"	The need for special PhV activities is assessed during the MAA procedure (obligatory). INN is not within the remit of the CHMP and beyond the scope of this guideline. Anyway, the same INN can be used only, if the product is confirmed to be a biosimilar. Regarding documentation of the prescribed epoetin in the patient file, CHMP has recently approved a specific wording to be included in the SPCs of all epoetins. Traceability is the responsibility of national authorities.
Line 226	**1**	**Comments:** Since prescription errors can have safety consequences for patients, we would recommend that difference in indication and/or route of administration be clearly stated on packaging materials so that reference and biosimilar can be used in	Self-evident for the product information. Packaging material is not the appropriate place. No need to include this in the guideline.

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		the same way. **Proposed change (if any):** ***Difference in indication and or route of administration with reference should be clearly mentioned on the packaging and package insert.***	
Line 226	**1**	**Comments:** Since the safety profile is not clearly linked to the epoetin receptor it is difficult to predict the potential for adverse events. A minimal study addressing major safety concern must be either assessed premarketing or pro-actively monitored post-marketing. In particular, for indications when the epoetin application is long and repeated and when patient is immune-compromised or may have a disturbance in immune system (MDS and HePC etc...) **Proposed change (if any):** ~~Since~~ **Although** the mechanism of action of epoetin is the same for all currently approved indications ***the safety profile cannot be systematically linked to epoetin / epoetin receptor interaction. Specifically, immunogenicity reaction and suspicion of tumour progression are not linked or not clearly linked to the epoetin receptor. Therefore it is recommended that a minimal clinical study addressing potential safety concerns is performed either pre-authorisation or through proactive post-marketing monitoring. In particular, in indications requiring long ESA exposure or in patient populations with immune-compromised status, it is recommended to specifically investigate the immunogenicity profile in the clinical setting.*** ~~and there is only one known epoetin receptor, demonstration of efficacy and safety in renal anaemia will allow extrapolation to other indications of the reference medicinal product with the same route of administration.~~	Not agreed. Pre-licensing studies are described in the guideline. If considered necessary, post-marketing studies will be requested by CHMP during the MAA procedure, based on the submitted data and the general knowledge on epoetins/the reference product at the given time. In addition, no studies can be requested for indications or populations for which the reference product is not licensed (such as MDS).
Line 231	**1**	**Comments:** ..there is only one known epoetin receptor: our interpretation of the current scientific discussion on this topic is that there may be alternative erythropoetin receptors: structure and nature of these receptors are, however, currently unclear and there is an ongoing discussion among experts in this field. There is published evidence that the mode of action of epoeitin and mediating receptor molecules are less clear than they appeared a few years ago.	The mechanism of action is the same for all currently approved indications of epoetins. For this the only one known erythropoietin receptor is responsible. The article by M. Brines mentioned by EBE relates to Epo derivatives, e.g. carbamylated Epo, that do not bind to the Epo receptor yet are tissue-protective in non-clinical studies. The investigators showed that

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		M. Brines, et al., "Erythropoietin mediates tissue protection through an erythropoietin and common beta-subunit heteroreceptor," Proc Natl Acad Sci U. S. A 101(41), 14907 (2004). http://www.ncbi.nlm.nih.gov/pubmed/15456912 *Wolfgang Jelkmann, et al., "The erythropoietin receptor in normal and cancer tissues," Critical Reviews in Oncology/Hematology 67(1), 39 (2008).* http://dx.doi.org/10.1016/j.critrevonc.2008.03.006	βcR is not required for erythropoiesis. This is clearly irrelevant for biosimilar epoetins and beyond the biosimilar discussion.
Line 234	**2**	The Note for Guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95) is cited in Line 94 and should therefore be added to the list references Please add: Note for Guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95)	Added.