The European Medicines Agency

SUBMISSION OF COMMENTS ON

Guideline on Similar Biological Medicinal Products containing biotechnology derived products as active substance: non-clinical and clinical issues Annex: recombinant Erythropoietin containing products EMEA/CHMP/945626/2005

Doc.Ref: EMEA/CHMP/BMWP/149141/2006

COMMENTS FROM

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GENERAL COMMENTS

Line no[1]. + paragraph no.	Comment and Rationale	Proposed change (if applicable)
	Introduction To add that "physico-chemical; and biological methods are available for characterisation of the protein"	Accepted
4.3	clinical efficacy studies 3 month treatment free period, is it long enough to prevent a "booster" when treatment is started again "Regardless of the endpoint definition, any relevant difference in the used dose would contradict the assumption of similarity – to this be specified by 90% confidence interval	Not Accepted: "Booster effect" not known for epoetin. Since this is an equivalence trial two-sided 95% CIs will be required for both co-primary endpoints.
6.	Phramacovigilance plan "For those indications where higher epoetin doses are required additional safety data should be generated" meaning is unclear, please specify, see also " 5 safety"	Accepted Such data should be generated as part of the pharmacovigilance plan. Will be clarified in guidance document.
1.	Introduction	Accepted

[1] Where available

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	Erythrpoietin is **mainly** produced in the kidneys Darpoetin has some amino acid changes to introduce extra glycosylation sites There is no evidence that the type of glycosilation influences the immunogenicity of epos	Proposal accepted since it has been demonstrated that erythropoeitin is also produced in liver, brain and uterus. It is known that glycosylation may affect immunogenicity of proteins.
2.	Toxicological studies No rationale for comparative repeat toxicity study, no predictive value for immunogenicity and long term toxicity since epos will be neutralised through antibodies No rationale for comparative local tolerance study	Not accepted <u>Rationale for repeat dose toxicity study (RDTS):</u> The whole comparability exercise is a stepwise procedure starting with the quality assessment and 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. As part of the overall comparability exercise, the RDTS provides information about comparability of non-clinical toxicological properties of similar biological medicinal product (SBMP) and reference medicinal product (RMP). Furthermore, the RDTS is designed to provide assurance that no ´unexpected toxicity` (e.g. toxic effects induced by process-related impurities) will occur after application of the ´new` recombinant erythropoietin to humans. ´Unexpected toxicity` cannot be excluded with sufficient certainty on basis of quality data alone, however, should be checked before starting clinical development. Immunogenicity:

		Determination of immune response in the RDTS covers two important aspects: (i) Since the mmunological mechanisms are expected to be sensitive to potential tructural differences between SBMP and RMP, determination of immune response in the RDTS will provide additional information about non-clinical comparability of SBMP and RMP (however, it is agreed that immune response in the RDTS is not predictive for immune response in humans since it also reflects consequences of application of a ´foreign` protein). (ii) Determination of (neutralizing) antibody formation provides, as essential part of the toxicokinetic evaluation, information whether sufficient exposure of animals to ´free` erythropoietin is achieved in the RDTS. The available experience shows that, despite antibody formation, the full range of pharmaco-toxicological effects of recombinant erythropoietin is usually revealed during a three-month RDTS. Rationale for local tolerance study The arguments presented for the RDTS (part of the overall comparability exercise, exclusion of unexpected toxicity) also hold true for the comparative local tolerance study.
4.3	Clinical efficacy studies Efficacy requirements (two studies, subsets) demand higher patient numbers than the phase III trials for the innovators	Not accepted. Not true. Most innovators have

		provided data on far more than 1000 patients pre-authorisation.
5.	Clinical Safety Safety database (300 patients) to small to exclude immunogenicity, what are the comparators? (Incidence of Ab formation for comparators is unknown) At least 12 to 24 immunogenicity data required, PRCA develop on average 14 month after start of treatment, (therefore 6 month efficacy data are not relevant). PRCA only develops after s.c. treatment and in non-cancer patients, therefore cancer and i.v. treated patients t exclude form immunogenicity studies Validated assay strategy is recommended (confirmatory assay, test for biologically)	Partially accepted The exact frequency of anti EPO antibodies (neutralising and non-neutralising) is not known for most products although Amgen states that it is close to 1% for its own rHuEPO (see Amgen comment below). It is difficult to provide an exact estimate of the size of the required immunogenicity database. Therefore, the annex will not state a specific number. Immunogenicity should be investigated sufficiently in the population and for the route of administration with the highest risk (renal anaemia patients and SC route of administration, respectively)
6.	Pharmacovigilance plan To concentrated on antibody formation and loss of efficacy and not waiting for full blown PRCA	Accepted We agree that if antibody-induced loss of efficacy can be demonstrated epoetin should be discontinued, if possible before full-blown PRCA has developed. Please note that this issue is beyond the scope of the guidance document.
SECTION 1: ***Paragraph 6***	Introduction Pure red cell aplasia (PRCA), due to neutralising anti-erythropoietin antibodies, has been observed in renal anaemia patients treated with subcutaneously administered epoetin, however, the spike in incidence of PRCA was only seen with epoetin alfa generated from one manufacturing source, and it is understood from recent publications that this was caused by a container/closure interaction. We therefore suggest the following amended wording of the last sentence (bolded & underlined and stricken out): *'Moreover, **a higher incidence of** pure red cell aplasia (PRCA), due to neutralising anti-erythropoietin antibodies, has been observed in renal anaemia patients treated with **certain** subcutaneously administered epoetin **alfa**. ~~Because~~ Antibody-induced PCRA is a very rare event and usually takes months to years of epoetin treatment to develop, **as** such, **these** events would be difficult to detect in pre-authorisation studies'.*	Not accepted All epoetins have the potential to cause antitibody-mediated PRCA and this is the important message that has to be brought across. This statement is important for the risk management plan that the applicant of a new epoetin will have to submit.
SECTION 3:	Non-clinical Studies	Not accepted

3.1 ***Paragraph 1***	**Pharmacodynamics studies** ***In vitro studies:*** *'In order to assess any alterations in reactivity between the similar biological medicinal product and the reference medicinal product, data from a* ***relevant*** ~~***number of***~~ *comparative bioassay (e.g. a receptor-binding study, cell proliferation assay), many of which may already be available from quality –related bioassays, should be provided'.*	Since the listed assays are expected to provide complementary information (e.g. receptor binding assays about receptor affinity; cell proliferation assays about ´intrinsic activity`), it is recommended to compile data from more than one *in vitro* assay.
3.2 ***Paragraph 1***	**Toxicological Studies** We suggest the following amended wording of the first sentence (bolded & underlined and stricken out): *'Data from at least one repeat dose toxicity study in a relevant species (e.g. rat, dog) should be provided. Study duration should be at least* ~~*3 months*~~ ***4 weeks'***.	The available experience shows that the full range of non-clinical pharmaco-toxicological effects of recombinant erythropoietins is usually revealed during a three month- but not during a 4 week-repeat dose toxicity study.
SECTION 4: **4.1**	**Clinical Studies** **Pharmacokinetic studies** The text as written represents highly sound science, but presents a practical problem with the current non-availability within the European Union of an epoetin-alfa reference product for subcutaneous administration. Thus the guideline should clarify that a single route of administration is acceptable. Accordingly, we propose the following amendment: "The relative pharmacokinetic properties of the similar biological medicinal product and the reference product should be determined in **a** single dose crossover study ~~ies.~~ using ~~**subcutaneous and**~~ intravenous administration. **If the subcutaneous route is to be included in the posology for the biosimilar epoetin, a separate single dose study should compare the pharmacokinetic and pharmacodynamic parameters for that product following subcutaneous vs. intravenous administration**.	Not accepted. The PK profiles for the SC route and the IV route of administration differ. Therefore, PK studies have to be performed for both routes of administration. As long as epoetin alfa is contraindicated for the SC use in renal anaemia patients it is preferable to choose a different reference product. Otherwise it is up to the applicant to develop a strategy to work around this problem. In the latter case, scientific advice is highly recommended..
4.3	**Clinical Efficacy Studies** The need to compare the biosimilar and reference products in *both* pre-dialysis *and* dialysis subjects would seem highly questionable, since there is no reason to believe that response sensitivity *and/or* dynamics will differ for the biosimilar epoetin product compared with the reference product. Bioequivalence of the biosimilar and reference products will be demonstrated in a preceding healthy volunteer PK/PD study.	Accepted We agree that it is not necessary to demonstrate efficacy and safety in both haemodialysis and pre-dialysis patients. The study proposals were made because epoetin therapy is usually started SC in the pre-dialysis phase of chronic renal insufficiency whereas the IV use should only be considered in

		patients on haemodialysis. Therefore, pre-dialysis patients are considered the appropriate patient population to be included in the titration phase study. Because of different dose requirements pre-dialysis and haemodialysis patients should not be mixed in the same study. Note: The term "bioequivalence" is not appropriate in the context of a similar biological medicinal products.
	We recommend a revision of section 4.3 as follows: *"Equivalent therapeutic efficacy between the similar and the reference product should be demonstrated in* ***an*** ~~***at least two***~~ *adequately powered, randomised, parallel group clinical trial.* *Confirmatory studies should preferably be double-blind to avoid bias. If this is not possible, at minimum the person(s) involved in decision-making (e.g. dose adjustment) should be blinded to treatment allocation.* *Sensitivity to the effects of epoetin is higher in erythropoietin-deficient than non-erythropoietin conditions and is also dependent on the responsiveness of the bone marrow. Patients with renal anaemia are therefore recommended as the target study population as this would provide the most sensitive model.* *The clinical trials should include* ~~***a 'titration phase' study during anaemia correction and***~~ *a 'maintenance phase' study in patients on epoetin maintenance therapy.* ~~***A 'titration phase' study is important to determine response dynamics and dosing during the anaemia correction phase. It should only include treatment naïve patients or previously treated patients after a suitably long epoetin-free period (at least 3 months).***~~ *The comparative phase should be at least 12 weeks in order to establish therapeutic equivalence of the similar and the reference product.* *The study design for a maintenance study should minimise baseline heterogeneity and carry over effect of previous treatments. It is recommended to include in a maintenance phase study, patients optimally titrated on the reference product (stable haemoglobin in the target range on stable dose and regimen) for at least three months. Thereafter, study subjects should be randomised to the similar or the reference product and followed up for at least three months. A longer period comparative phase (e.g. 6 month) will be needed if baseline treatment heterogeneity and carry over effects cannot be excluded.* *To avoid confounding factors, participating patients in either study should not have been receiving red blood cell transfusions for an appropriate length of time prior to the treatment phase.* *In the course of these studies, epoetin doses should be closely titrated to achieve and maintain haemoglobin*	Similar efficacy and safety of the 'similar' and the reference medicinal product should be shown for the titration phase and the maintenance phase as well as for different routes of administration. The focus of the titration phase study is on response dynamics and related adverse events. The maintenance phase study is more sensitive to show differences in efficacy. Since dosages differ for IV and SC use, both routes of administration should be investigated separately. Therefore, a minimum of two clinical trials is necessary for demonstration of similar efficacy and safety. We agree that it is not necessary to demonstrate efficacy and safety in both haemodialysis and pre-dialysis patients. The study proposals were made because epoetin therapy is usually started SC in the pre-dialysis phase of chronic renal insufficiency whereas the IV use should only be considered in patients on haemodialysis. Therefore, pre-dialysis patients are considered the appropriate patient population to be

	concentrations. The protocol should clearly pre-define the haemoglobin changes that will demand ~~***a change in***~~ ***an adjustment of*** *the dose of epoetin.* ***The sponsor should justify the choice of primary endpoint: this could be based on equivalence of the mean haemoglobin or haematocrit level, or on*** ~~***. Preferably, 'haemoglobin responder rate' (proportion of patients achieving a pre-specified haemoglobin target in the 'titration phase study') or***~~ *'haemoglobin maintenance rate' (proportion of patients maintaining haemoglobin levels within a pre-specified range in the 'maintenance phase' study)* ~~***and epoetin dosage should be co-primary endpoints***~~*. The fact that* ***the*** *epoetin dose is titrated to achieve the desired response reduces the sensitivity of the haemoglobin-targeted endpoints to detect possible differences in the efficacy of the treatment arms. The need* ~~***of***~~ ***for*** *combined end points should therefore be considered* ~~***but knowing***~~ ***bearing in mind*** *that this reduces the sensitivity of* ***the*** *trial. Regardless of the endpoint definition, any relevant difference in the dose used* ***for a given route of administration*** *would contradict the assumption of similarity.* *Transfusion requirement should be included as* ***a*** *secondary endpoint.* ~~***Due to different epoetin doses necessary to achieve target haemoglobin level in pre-dialysis and dialysis patients, these two populations should be investigated in separate studies.***~~ Therapeutic equivalence has to be demonstrated for both routes of administration. This is best achieved by performing separate studies (e.g. a 'titration phase' s.c. study in a pre-dialysis population and a 'maintenance phase' i.v. study in a haemodialysis population)".	included in the titration phase study. Because of different dose requirements pre-dialysis and haemodialysis patients should not be mixed in the same study. Responder rate as well as mean change in Hb has been used as primary endpoint in clinical trials. This will be reflected in the guidance document. The guideline will state that haemoglobin target range and titration schedule should be in accordance with current clinical practise. .
SECTION 7:	Extension of Indication We are very pleased to acknowledge section 7 regarding the extension of indication of the reference product. Given that the mechanism of action of erythropoietin is identical regardless of disease state or route or administration, we understand this to mean that appropriate demonstration of efficacy and safety in renal failure patients, will be sufficient to gain an extension indication for use of erythropoietin in the treatment of chemotherapy patients, and would therefore propose a strengthening of this statement as follows: *Appropriate demonstration of efficacy and safety in the most sensitive clinical model (renal failure), may allow extension to other indications of the reference product if the mode of action is the same and if appropriately justified by current scientific knowledge.* ***On the basis of existing scientific knowledge, and on the understanding that the mechanism of action of erythropoietin is identical regardless of disease state or route of administration, adequate demonstration of safety and efficacy in renal failure patients will allow extrapolation to an indication for use in adult chemotherapy and surgical patients.***	Half accepted We agree that extrapolation may be possible to indications for which the mechanism of action of epoetin is the same. However, we believe that the current wording is appropriate.
1.	**Introduction** …. The rate of haemoglobin increase may vary considerably between patients and is dependent not only on the dose of epoetin but also other factors such as iron stores, baseline haemoglobin and erythropoietin levels, and the presence of concurrent medical conditions.	Will be included.

1.	…. Because antibody-induced PRCA is a very rare event and usually takes months to years of epoetin treatment to develop, such events are difficult to be identified in pre-authorisation studies.	Accepted
2.	**Scope** This product specific guidance as an Annex to the above guideline presents the current view of the CHMP on the application of the guideline for demonstration of comparability between two recombinant human erythropoietin medicinal products. …	Accepted
3.	**Non-clinical studies** Before initiating clinical development, non-clinical studies should be performed. These studies should be comparative in nature and should be designed to detect differences in the biological response between the similar biological medicinal product and the reference medicinal product and not just the response *per se*. The approach taken will need to be fully justified in the non-clinical overview.	Accepted
4.	Clinical studies 4.3 Clinical efficacy studies Equivalent therapeutic efficacy between the similar and the reference product should be demonstrated in at least two adequately powered, randomised, parallel group clinical trials. If multiple unrelated indications are to be sought, it is recommended to study at least two unrelated indications e.g., renal anemia (deficiency) and cancer chemotherapy induced anaemia (non-deficient)	Not accepted Extrapolation may be possible. See comments above.
4.3	Confirmatory studies should preferably be double-blind to avoid bias. If this is not possible, at minimum the person(s) involved in decision-making (e.g. dose adjustment) should be blinded to treatment allocation. Sensitivity to the effects of epoetin is higher in erythropoietin-deficient than non erythropoietin-deficient conditions	Not accepted We believe that both criteria are important to identify the most sensitive population.
4.3	The fact that epoetin dose is titrated to achieve the desired response reduces the sensitivity of the haemoglobin- related endpoints to detect possible differences in the efficacy of the treatment arms. The need of combined end points should therefore be considered Regardless of the endpoint definition, any relevant difference in the used dose would contradict the assumption of similarity. Transfusion requirement should be included as a secondary endpoint…….	Accepted
4.3	Therapeutic equivalence has to be demonstrated for both routes of administration. This is best achieved by performing separate studies (e.g. a 'titration phase' s.c. study in a pre-dialysis population and a 'maintenance phase' i.v. study in a haemodialysis population). Acceptable difference between the investigational product and the reference product for target haemoglobin and erythropoietin dose should be determined and specified 'a priori' and serve as the basis for powering the study.	Accepted
7.	**Extension of indication** Appropriate demonstration of efficacy and safety in the most sensitive clinical model (renal failure), may allow extension to other indications of the reference product if the mode of action is the same and if appropriately justified by current scientific knowledge (see also section 4.3 Clinical efficacy studies).	Cross reference not applicable
	The draft guideline on erythropoietin should explicitly state that the starting point for undertaking the evaluation of similarity should be that the biosimilar erythropoietin is different to the reference product with respect to nonclinical and clinical attributes. This being the case, the preclinical and clinical research program must allow conclusions to be made about the similarity of the candidate biosimilar erythropoietin to the appropriate reference product.	Accepted It is principally agreed that two epoetins are considered different until proven otherwise. This is the reason why a comprehensive comparability

		exercise is required.
	The data package proposed in the draft guidance on erythropoietin is insufficient to provide the necessary assurance regarding similarity of efficacy and safety of a biosimilar erythropoietin across all indications, routes of administrations and the approved dose range currently licensed for the originator products. If the renal failure studies are the only comparative clinical studies required to define the efficacy characteristics of a biosimilar erythropoietin, these studies need to be rigorously designed to ensure that a conclusion of equivalent therapeutic efficacy can be extrapolated with confidence to other clinical settings. Amgen recommends that more detailed guidance be provided on the study design for renal failure studies, including definition of therapeutic response, equivalence margins, and proposals for management of dose changes.	Partially accepted Therapeutic response may be defined in different ways e.g. as "responder rate" or "mean change in Hb" It is principally up to the applicant to provide and appropriately justify definitions of therapeutic response or equivalence margins. The Haemoglobin target range and titration schedule should be in accordance with current clinical practise. In an equivalence study the algorithm for dose adjustment should always be the same for both treatment arms. Some more detailed information on these issues will be considered.
	An appropriately sized and generalisable safety database for biosimilar erythropoietin is required pre-approval. This database should be based on clinically reasonable risk tolerance considerations that will allow appropriate evaluation of the safety profile in comparative studies. There are substantial differences between the renal and oncology indications, including differences in dose requirements, commonly used routes of administration, and adverse event profiles. In addition, the proposed safety database has a large degree of heterogeneity.	Partially accepted Most AEs (such as hypertension, access-thrombosis) are often related to exaggerated pharmacodynamic response. Common events can be adequately assessed in the proposed clinical trials. In addition. epoetin is titrated according to Hb response. Immunogenicity is best assessed in patients with renal anaemia, which is the suggested patient population. Additional safety data will be required post-marketing.
	The exclusion of a specified rate of immunogenicity, such as 0.25%, should be required before approval. An assumption of comparable immunogenicity of biosimilar erythropoietin to the reference product cannot be the base hypothesis for approval. The proposed database of 300 patients, which cannot exclude a rate of immunogenicity of 1%, is insufficient to achieve the guideline's stated aim of excluding "excessive" immunogenicity.	The exact frequency of anti EPO antibodies (neutralising and non-neutralising) is not known for most products. It is therefore difficult to provide an exact estimate of the size of the required immunogenicity database. Consequently, the guideline will not state a specific number
2.	<u>Scope</u>	Not accepted

	The following amendments should be made to the text of the draft guideline: "……..The final set of studies necessary to fulfil nonclinical and clinical requirements for a given medicinal product will be determined by data generated by the comparability exercise itself. The nonclinical and clinical requirements defined in this guideline should be regarded as a minimum requirement for approval."	We believe that the guideline is clear in that respect.
2.	The nonclinical and clinical studies defined in this guideline should be considered as a minimum requirement for the approval of a biosimilar erythropoietin. ….. The draft guidance on erythropoietin should state clearly that, if there are important differences between the biosimilar erythropoietin and the reference product, the biosimilar erythropoietin cannot be approved as a biosimilar medicine.	See comment above. We believe that it is self-evident that a medicinal product, which does not fulfil the requirements for "biosimilarity" cannot be approved as a "biosimilar" product.
3.	Nonclinical Studies .Pharmacodynamic Studies PK and PD data from toxicology studies using suprapharmacological doses of erythropoietin, as currently recommended, cannot be considered acceptable for a preclinical comparability assessment of PK/PD profiles. Specific preclinical PK/PD studies at a relevant dose range should be considered as a prerequisite for an assumption of similarity prior to the initiation of the clinical trial programme. There are a number of concerns regarding the use of data from a toxicology study to assess pharmacodynamic response of erythropoietin. A PK or PD difference may be masked as a result of the very high doses used in the toxicology study. For this reason, characterisation of the dose-exposure-response relationship is warranted, and should include preclinical PK assessment.	Partly accepted The NfG adopted by the CHMP in March 2006 recommends a comparative evaluation of PD effects of similar biological medicinal product and reference medicinal product in ´*in vivo*` studies such as the polycythaemic or normocythaemic mouse assay. Furthermore, the NfG points out that additional information on the erythrogenic activity may be obtained from the repeat dose toxicity study (RDTS). This is due to the fact that the main non-clinical toxicological effects of recombinant erythropoietin are related to an (exaggerated) PD effect on the bone marrow. With respect to the concern about the use of ´suprapharmacological` doses in the RDTS, the ´NfG on repeated dose toxicity` (CPMP/SWP/1042/99) points out that the low dose should be sufficient to produce a PD (therapeutic) effect or result in a systemic exposure

		comparable with that expected in the intended clinical use.
3.2	Toxicological Studies The following amendment should be made to the text of the draft guideline: "Data from at least one repeat dose toxicity study in the beagle dog should be provided. The study should include the reference product as a comparator arm. Study duration should be at least 3 months with a 28 day treatment-free recovery period." Consistent with the recommendation from the CHMP in section 3, that nonclinical studies should be comparative in nature, that is, using reference product as an active control, This requirement should be repeated in the recommendations for the design of the repeat dose toxicity study. Therepeat dose toxicity study include a 28-day treatment-free recovery period and that this requirement should be included in the guideline. This recommendation will enhance the capability of detecting antibodies to the biosimilar erythropoietin that may be masked by the exaggerated drug levels during the treatment phase, and is consistent with the guideline's special emphasis to determine any immunogenic responses. Furthermore, as this study will likely be the only nonclinical safety assessment conducted prior to human studies with the biosimilar erythropoietin, a recovery period will allow an assessment of resolution of toxicities observed during the treatment phase. The beagle dog should be considered the relevant species, since the half-life of red blood cells in dogs (60 days) is similar to humans with chemotherapy-induced anaemia (60 to 80 days) (Hematology 4th Edition, 1990). The half-life of red blood cells in rats is approximately 30 days.	Not accepted Comparator arm: It is agreed that the repeat dose toxicity study (RDTS) should include the reference product as a comparator arm. However, since the introductory paragraph of the non-clinical section of the NfG clearly expresses that the non-clinical studies in general should be comparative in nature, a repetition of this recommendation for the RDTS does not appear to be necessary. Treatment-free recovery period The available experience shows that the non-clinical toxicity of recombinant erythropoietin can sufficiently be characterized by a 3-month RDTS. A 28-day treatment-free recovery period is not expected to provide significant additional information. Relevant species It is agreed that physiology of red blood cells in dogs is more similar to the human situation than that of rat red blood cells. However, since the rat has been shown to be responsive to the erythrogenic effects of recombinant erythropoietins and since, as expressed in NfG, the non-clinical studies should be designed to detect differences in the pharmaco-toxicological response between similar biological medicinal product and

		reference medicinal product rather than the response *per se*, the rat appears to be an appropriate species for the RDTS and may even be advantageous, taking into account animal protection aspects.
4.	Clinical Studies Epoetin alfa and epoetin beta have a well-established efficacy and safety profile in a number of clinical settings (oncology, nephrology, HIV/AIDS, anaemia of prematurity) and associated dosage ranges and routes of administration, intravenous (IV) and subcutaneous (SC). By definition, a biosimilar erythropoietin offers no incremental clinical benefit compared with the reference product, as it must be shown to have an equivalent efficacy profile. Consequently, there should not be any diminished benefit or significant increased risk with the biosimilar erythropoietin.	Agreed
4.	Given that the current guideline permits possible extrapolation between disease settings, we have attempted to provide recommendations identifying specific areas of concern There are several clinically important differences between the erythropoietin indications. Subtle differences in the pharmacokinetic or pharmacodynamic performance of a biosimilar erythropoietin could have clinically important consequences. If extrapolation from the renal failure setting is to be permitted, pharmacokinetic and pharmacodynamic studies should be conducted over the entire dose range of erythropoietin that is used in the indications to which extrapolation is sought.	Not accepted One comparative single dose PK/PD study for each route of administration is considered sufficient to determine the relative PK and PD profile of the 'similar' and the reference product. The selected dose should be in the linear ascending part of the dose-response curve
4.	As the renal failure studies are proposed as the only comparative clinical studies to define the efficacy characteristics of a biosimilar erythropoietin, these studies need to be rigorously designed to ensure that the conclusion of equivalent therapeutic efficacy can be extrapolated with confidence to other clinical settings.	Accepted
4.	Given the differences between the renal and oncology populations in terms of dose requirements, commonly used routes of administration and adverse event profiles, as well as the degree of heterogeneity in the proposed safety database, Amgen recommends that a generalisable safety database of appropriate size, derived from patients receiving the biosimilar erythropoietin, should be required pre-approval.	See comment above
4.1	Pharmacokinetic Studies "The relative pharmacokinetic properties of the similar biological medicinal product and the reference product should be determined in single dose crossover studies using subcutaneous and intravenous administration over the entire dose range of the reference product. ….."	Not accepted See comment above
	Pharmacodynamic Studies "Reticulocyte count and haemoglobin ~~is~~ are a relevant pharmacodynamic markers for the activity of epoetin and	

	recommended to be used in comparative pharmacodynamic studies and should be included as part of the single dose pharmacokinetic study in healthy volunteers. On the other hand, reticulocyte count is not an established surrogate marker for efficacy of epoetin and therefore no suitable endpoint in clinical trials."	Half accepted In single dose studies, reticulocyte count is the most relevant and preferred PD marker.
4.3	Clinical Efficacy Separate the guidance for the suggested titration and maintenance studies to provide clear information regarding study design.	Not accepted No more separation considered necessary but rewording for clarity.
4.3	**Titration Study** Discuss the impact of the contraindication for SC dosing for Eprex (Epoetin alpha) with respect to the limitations of an Eprex control group for the titration study.	Not accepted Beyond the scope of this guidance document. In addition, contraindication may be reversed (also see comment above)
	Provide more specific detail regarding study design, acceptability of licensing endpoints, analytical testing procedure and equivalence margins.	See comment above
	The study objective and hypothesis for the titration study should be clearly stated in this section and the design requirement clearly defined as a therapeutic equivalence study with appropriate reference to ICH E9 guideline regarding statistical principles for clinical trials.	Not accepted ICH E9 and E10 are already included in the reference list. It is not intended to repeat statistical principles discussed in these guidelines
	The proportion of patients with a "therapeutic response" is an acceptable endpoint in principle. However, specific details regarding therapeutic response definition, and the timeframe at which response should be measured should be provided. In addition, instruction for handling patient attrition, missing data and the confounding influence of transfusions should be provided.	Partially accepted Comment will be taken into consideration. However, since therapeutic response can be defined in different ways, the guideline should only outline the principles and problems and should not give an exact recipe how studies have to be performed. It is agreed that the study design should take current clinical practise into consideration.
	Based on the current recommendation for primary endpoints (i.e. the proportion of patients achieving a therapeutic response) the equivalence margins should be stated and the level for testing clearly defined. Based on discussion with the clinical community and deep research knowledge in the field, Amgen suggests ± 10% as a logistically feasible and clinically acceptable margin for equivalent therapeutic efficacy with statistical assessment using a two-sided 95% confidence interval.	Not accepted Principally, the applicant should determine and appropriately justify equivalence margins taking into account the data obtained with the reference product and, if appropriate, with other epoetins. More experience is

		needed before definite equivalence margins can be set.
	Demonstration of equivalent therapeutic efficacy cannot be assumed if either significant dose changes (for either hyper-response or hypo-response) or significant differences in transfusion requirements are observed. Consideration of these key endpoints should be addressed in the guidance document.The guidance for the proposed titration study does not specify co-primary endpoints for dose or transfusion requirements, these are key factors in determining equivalent therapeutic efficacy, and any signal that transfusion requirements differ between the biosimilar erythropoietin and reference product needs to be carefully evaluated prior to accepting a conclusion of equivalent therapeutic efficacy. While we do not believe that equivalence for dose or transfusion requirements needs to be formally demonstrated (or margins specified) in the anaemia correction setting in renal disease, the guideline should be explicit in stating that if statistically significant differences in overall dose or differences in transfusion requirements are observed, then equivalent therapeutic efficacy cannot be concluded. Furthermore, for this study in particular, due to the subjective nature of the decision to transfuse, blinding should be further emphasised in this section of the guideline.	Accepted We agree that markedly different dose requirements would contradict the assumption of similarity. Since Hb is a titrated endpoint we suggest that a Hb-related parameter and dose requirements be co-primary endpoints in both the titration phase and the maintenance phase studies. Appropriately justified equivalence margins should be provided for both primary endpoints.
	Maintenance Study The study objective and hypothesis for the maintenance study should be clearly stated in this section, and the design requirement clearly defined as a therapeutic equivalence study, with appropriate reference to ICH E9 guideline regarding statistical principles for clinical trials.	Not accepted ICH E9 and E10 are already included in the reference list.
	The co-primary endpoints are required to assess equivalent therapeutic efficacy in the proposed maintenance trial. However, we further recommend more detailed specification regarding the exact definition of these co-primary endpoints. To ensure clinical relevance, the Hb target range should be defined. This range could be based on current European Best Practice Guidelines for the treatment of anaemia in renal failure patients (ie 11 to 12 g/dL) or otherwise justified. Any proposed deviation from this target range should be clearly justified and agreed via scientific advice procedure before the implementation of the study. **The evaluation period should be clearly defined. To ensure that variability in both Hb and dose can be adequately characterised, the minimum requirement for Hb assessment should be sequential weekly values over a minimum evaluation period of 8 weeks.**	Partially accepted The guideline with state that haemoglobin target range and titration schedule should be in accordance with current clinical practise. Principally, the co-primary endpoint 'dose requirement' can be expressed in different ways, e.g. as mean weekly dose during a pre-specified period of the comparative phase or as cumulative dose. The applicant should appropriately justify the chosen endpoint and the time point of assessment.
	Based on the current recommendation for co-primary endpoints (i.e. the proportion of patients maintaining Hb target range and dose requirements), the equivalence margins should be stated, and the coverage of the confidence intervals clearly defined. ± 10% limits for the proportion of patients maintaining Hb target range as a logistically feasible and clinically	See comment above.

	acceptable margin for therapeutic equivalence, using a two-sided 95% confidence interval of the difference.	
	Clear details regarding the statistical basis for the study and in particular, the testing procedure for co-primary endpoints should be provided	Not accepted This is beyond the scope of the current guideline. A reference to Guidelines ICH E9 and E10 are included. Other relevant references may be included.
5	Clinical Safety To confirm comparable safety profiles for known events of interest and that no important differences exist in the proportion of patients exceeding Hb levels/rates of rise, defined in the current SPCs for safety reasons, larger comparative trials in both correction of anaemia and Hb maintenance than currently recommended should be conducted prior to approval.	Not accepted The guideline does not propose a specific sample size. The clinical trials will have to be powered for both co-primary endpoints to ensure that similar response is achieved with similar epoetin doses.
	It is critical that the pre-approval safety database allows for adequate characterisation of both the rate of rise in Hb during the correction of anaemia and the ability to adequately control Hb below the specified upper thresholds before confidence regarding the clinical similarity of the reference and biosimilar erythropoietin safety profile can be confirmed in order to allow extrapolation to other clinical settings. Based on the current proposal, there will be insufficient data to characterize the hyper- and hypo-responsive subset of patients most at risk, consequently precluding extrapolation to other clinical settings, particularly oncology where the doses are considerably higher than used in the renal setting.	Not accepted The clinical studies will need to be adequately powered. With a too low sample size it will not be possible to demonstrate comparable efficacy with sufficient confidence. Regarding extrapolation to other indications see comment above.
	The increase in patient numbers from the 300 currently declared in the draft guideline will allow for a sufficiently comprehensive assessment of safety, particularly with respect to potential differences in the proportion of patients exceeding known thresholds for Hb level and rate of Hb increase that are defined in the current SPCs for erythropoietic therapies:: "Safety data from at least ~~300~~ 700 patients treated with the similar biological medicinal product ~~in the efficacy~~ from comparative trials (preferably blinded to avoid reporting bias) is considered sufficient to provide an adequate pre-approval safety database. ~~and to exclude excessive immunogenicity~~ Particular attention should be paid to the comparison of adverse events described in the current SPC of the reference product."	Not accepted The proposed minimum size of the safety database appears too large. No specific number will be given in the guidance document (see comment above).
	The guideline should provide more details regarding the validated assay methodology required for the detection of both binding and neutralizing anti-erythropoietin antibodies	Not accepted The biosimilar guidelines already state that antibody assays should be validated and highly sensitive. Antibodies will have to be further evaluated for binding or neutralizing capacity. Appropriate documentation

		will have to be provided. Providing detailed assay methodology is beyond the scope of the guideline.
	The following amendments should be made to the text of the draft guideline: "The applicant should provide at least 12 months immunogenicity data in at least 1000 patients treated with the similar biological medicinal product to exclude excessive immunogenicity. The immunology database can be derived from the comparative trials used to demonstrate clinical efficacy, however, it should include at least 500 patients treated with the SC route of administration." PRCA due to anti-erythropoietin antibodies induced by drug administration represents a potentially life long or fatal adverse reaction. Considering there are effective alternatives that have not shown a similar increase in antibody-mediated PRCA as previously seen with Eprex, it is incumbent upon the sponsor of a biosimilar erythropoietin to clearly demonstrate the absence of immunogenicity with their product. Despite low rates of immunogenicity observed over the last 15 years, it cannot be assumed that biosimilar erythropoietins will have a similar profile. Given the lack of certainty regarding the cause(s) of the increase of cases with Eprex, the precautionary principle needs to be applied regarding possible immunogenic differences between the biosimilar erythropoietin and the reference product. The pre-approval safety database for a biosimilar erythropoietin should be sized to exclude the possibility of a greater than 2 fold increase in the relative risk of binding antibodies (i.e. approximately 1000 patients be tested at baseline and after 6 and 12 months of treatment) and that all binding antibodies should be without neutralizing activity against erythropoietin. Importantly, if insufficient numbers of patients (eg less than 500 patients) are treated with the SC route of administration, consideration should be given to limiting the route of administration to IV only until such time that sufficient clinical data regarding the SC use could be provided. The difference between this number and the sample size for the safety database generated through the therapeutic equivalence trials could be closed with non comparative trial(s) in the anaemic renal failure population, by using the SC route administration.	Not accepted The proposed size of the pre-authorisation immunogenicity database is considered too high and exceeds that presented for some innovator products (see EPAR on Dynepo). The exact antibody frequency of most epoetins (neutralising and non-neutralising) is not known and also depends on the sensitivity of the assay (the frequency of about 1% stated by Amgen is based on a highly sensitive assay). It is difficult to provide an exact estimate of the size of the required immunogenicity database. Therefore, the annex will not state a specific number. We agree that any neutralizing antibody detected in the pre-authorisation phase would be a serious safety concern.
	Pharmacovigilance Plan The sponsor must present a Pharmacovigilance Plan that is acceptable to competent authorities, and which continues to address potential concerns regarding immunogenicity and potential rare serious adverse events. Post approval safety commitments should be required to establish the product safety profile for rare events and events potentially associated with longer latency. Special attention should be paid to immunological adverse events in patients with chronic administration, such as PRCA. A comprehensive post-marketing safety surveillance system should be established to detect these events. Based on safety issues or concerns observed for both the reference products and in the biosimilar erythropoietin safety database,	Accepted Generally, the requirements for the pharmacovigilance /risk management plan will be based on the clinical safety experience for the reference product, the product class and the safety data obtained for the medicinal product for which marketing authorisation is sought. .

	a list of events requiring heightened safety surveillance should be established, and standardized templates should be employed to support comprehensive data collection, review, and follow-up in order to determine long term outcomes. Contact telephone information should be represented in the SPC to facilitate ease of spontaneous adverse event reporting. An effective risk communication procedure should be established to communicate new observations from the company to regulatory authorities, physicians and patients.	
	Extension of Indication Provide greater details regarding the ability to extrapolate between indications and define the specific criteria necessary to allow extrapolation from the renal setting to all other indications (including paediatric and oncology settings), doses and routes of administration. The current guideline requires significant modification and a far greater degree of detail to provide confidence regarding the scientific evidence that would be required to permit extrapolation. Our major recommendations include: evaluation of PK over the entire dose range of erythropoietin; adherence to robust study design principles; rigorous definition of equivalence margins for the efficacy studies in the renal populations; and a larger comparative safety database that permits characterisation of hypo- and hyper-response to the biosimilar erythropoietin and reference products. In particular, we do not believe - given the heterogeneity of the proposed populations and posologies, the diverse clinical indications, duration of therapy, routes of administration and critically, the 5-fold difference in dose between the oncology and predialysis settings - that it is appropriate to extrapolate safety data between the renal and oncology settings based on the pre-approval programme outlined in the current draft of the guideline.	Not accepted One comparative single dose PK and PD study for each route of administration is considered sufficient to determine the relative PK and PD profile of the 'similar' and the reference product. The selected dose should be in the linear ascending part of the dose-response curve. Appropriate demonstration of efficacy and safety in the most sensitive clinical model (renal failure) may allow extension to other indications of the reference product if the mechanism of action is the same and if appropriately justified by the applicant.
1.1	**Erythropoietin** Erythropoietin presents one of the most difficult and complex cases for development of requirements for establishing the safety and efficacy of similar biological medicinal products. There are currently different erythropoietin-based products authorized in the European Union, …There are differences in the potencies, dosage regimens, approved routes of administration and indications of the products. Thus, the innovative products are not freely interchangeable in the manner of generic drugs from different sources, especially in respect of dose equivalence. Appropriate measures must be taken when switching patients from one product to another (e.g., tracking the particular product given to the patient). Any claim concerning interchangeability of an erythropoietin product that is claimed to be similar to one already marketed, therefore, would have to be substantiated with appropriate clinical trials demonstrating dose equivalence.	The issue of interchangeability is beyond the scope of the intended guidance document. Traceability is addressed in the general guideline.
	It is also generally accepted that subtle differences in the active substances, dosage forms and other characteristics can significantly affect the safety and efficacy of erythropoietin products. Patterns of glycosylation that differ from one cell line to another are, for example, known to affect therapeutic performance. However, the exact relationship of different glycosylation patterns to clinical effects is not known, and it is not possible to predict what therapeutic effects such differences will have.	Accepted

	Even more important, changes in the finished dosage form, not involving any change in cell lines or the manufacture of the active substance, have been associated with occurrence of serious, albeit rare, immunogenic effects, leading to pure red cell aplasia (PRCA) in some patients. This condition, which affects endogenous erythropoietin as well as patient response to other forms of erythropoietin therapy, is qualitatively different from other immunologically mediated events, such as reduced efficacy of a specific product due to development of neutralizing antibodies, or rare anaphylactic events associated with specific products. While all such risks must be addressed, a risk of a condition such as PRCA warrants special attention.	Agreed
1.2	**Principles for Evaluating Products Claimed to be Similar** We urge that the following principles be applied to the development of any product claiming to be similar to an authorized erythropoietin product: Each applicant should be required to justify the development strategy for its product in the marketing authorization application. The requirements will depend on the clinical/safety experience available for the product class and the therapeutic area, but the endpoint in each case must be an appropriate demonstration of safety and efficacy equivalent to the reference product.	Accepted
	Principles for Evaluating Products Claimed to be Similar We urge that the following principles be applied to the development of any product claiming to be similar to an authorized erythropoietin product: As the CHMP has already recognized in its Guideline on Similar Biological Medicinal Products (CHMP/437/04) and the draft Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (EMEA/CHMP/42832/2005), each company developing an erythropoietin product under the procedures for similar biological medicinal products 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.	Accepted The general guideline states that the same reference product should be used for all aspects of the comparability exercise
	Principles for Evaluating Products Claimed to be Similar We urge that the following principles be applied to the development of any product claiming to be similar to an authorized erythropoietin product: Competent authorities should require full information on the quality aspects of investigational products, appropriate non-clinical studies evaluating potential risks to humans and other information necessary to conclude that it is safe to initiate clinical trials. Similar biological medicinal products differ significantly from ordinary generic drugs, which generally contain a single active molecule that can be fully identified and characterized and whose identity can often be satisfactorily shown by compliance with requirements of a compendial monograph. Monographs in the *European Pharmacopoeia* and national pharmacopoeias cannot be applied for this purpose in the case of recombinant DNA-derived protein products due to their complex structure and the fact that they generally comprise a family of molecules with characteristics that differ depending on cell lines and post-translational modifications.	Accepted A full quality dossier will be required and a comprehensive comparability exercise with the reference product. This is the key for the next stage of the development process. Before going into clinical development, comparative non-clinical studies should be performed. Appropriate guidance will be given.
	Principles for Evaluating Products Claimed to be Similar We urge that the following principles be applied to the development of any product claiming to be similar to an	Accepted It is agreed that, for the time being,

	authorized erythropoietin product: Special attention must be paid to differing patterns of glycosylation. In general, different versions of the erythropoietins claimed to be similar to reference products within the scope of the draft Guidance are likely to have the same polypeptide structure and sequence (although this must, of course, be demonstrated). But it is highly unlikely that a product claimed to be similar will have the same glycosylation and isoform pattern as the reference product. …. physico-chemical tests will never be sufficient to demonstrate "similarity" of erythropoietin products, and that substantial programs of preclinical and clinical testing will be required.	analytical tools are not sufficient. Therefore, clinical trials are required.
	Principles for Evaluating Products Claimed to be Similar We urge that the following principles be applied to the development of any product claiming to be similar to an authorized erythropoietin product: A company submitting an application for a similar biological medicinal product will not have access to information concerning the manufacturing processes for the reference product. Therefore, a comparability exercise between a similar biological product and a reference product is impossible. Instead, it will be necessary for the applicant to provide full information on all aspects of its own manufacturing process for the investigational product that is claimed to be similar. This information must be assessed in the same manner as would be done for an approved innovative product, with appropriate attention to process development and other manufacturing and quality issues.	Accepted A full quality dossier will be required. (see comment above)
	Principles for Evaluating Products Claimed to be Similar We urge that the following principles be applied to the development of any product claiming to be similar to an authorized erythropoietin product: To protect patient safety, pivotal clinical trials should not be permitted until early-phase trials have been conducted to determine the appropriate dose and evaluate safety. Although legal responsibility for evaluation of clinical trial applications will remain with the member states, many national competent authorities will lack the expertise required to perform this function adequately for similar biological medicinal products. It may be necessary for the EMEA to play a coordinating role, perhaps through the CHMP scientific advice process. The ethical implications of early clinical trials in patients should be seriously considered.	Not accepted The first step of the clinical comparability exercise is the demonstration of similar PK profiles. Dose finding studies are not necessary because the same posology for the similar and the reference medical products will be used in the subsequent clinical 'equivalence trials'.
	Principles for Evaluating Products Claimed to be Similar We urge that the following principles be applied to the development of any product claiming to be similar to an authorized erythropoietin product: Each indication for which similarity is claimed must be separately demonstrated, as required by section 4 of Part II of Annex I to Directive 2001/83. This is especially important for the various indications of erythropoietin, because the causes of anemia differ in the indications, as do the dosing regimens to correct anemia. For example, in chronic renal disease, the kidneys do not produce enough erythropoietin to maintain normal hematocrit, but the hematopoietic system is quite capable of producing normal levels of red blood cells if erythropoietin is administered. In contrast, cancer patients produce normal levels of erythropoietin, but their hematopoietic system is impaired due to the effects of chemotherapy, so that large doses of erythropoietin are needed to support production of normal levels of red blood cells. For these and other reasons, a separate comparative clinical trial will be needed for each indication.	Not accepted The requirements for safety and efficacy will depend on the claimed therapeutic indications. 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. However, this is a case by case decision. For erythropoietin, the mechanism of action is the same in all currently approved indications. Therefore, if efficacy and safety has been demonstrated in the most sensitive model (renal anaemia) extrapolation to the other indications of the reference product may be possible.
	Consideration should be given to the need for studies of naïve patients, especially when evaluating immunogenicity. The clinical data suggest that most patients who developed PRCA did so within the first year of exposure. This is consistent with the general understanding that patients who have been on a pharmaceutical protein are less likely to develop an immune response than previously untreated patients	Accepted Due to the nature of the requested clinical trials both treatment naïve and 'transfer' patients will be included in the immunogenicity assessment. One-year data will be required pre-authorisation
	When comparative studies are carried out using patients previously stabilized on erythropoietin therapy, it is important that the erythropoietin product with which they were previously treated is the same as that used in the comparative study.	Partially accepted Patients may have received a different epoetin previously. Such patients would be eligible if they have been "treatment-free" for an appropriate period of time, e.g. 3 months to participate in a "correction phase" study) or have been switched to and optimally titrated on the chosen reference product for at least 3 months (Maintenance phase study). Only one reference product should be used for the whole comparability exercise.
	If sufficient numbers of patients previously stabilized on erythropoietin therapy cannot be identified for comparative clinical trials in the EU, care must be taken to insure that patient populations from other regions are appropriate. For example, if patients have previously received forms of erythropoietin that are not used in the EU, it may be necessary to consider whether data from those patients are fully applicable to the European clinical situation or can support valid comparative clinical trials with a reference product authorized in the EU. In these patients, the issue of immunogenicity has to be considered.	Accepted Appropriateness of data generated outside the EU has to be considered for any clinical trial, not just for 'biosimilar' applications.
	Great care must be taken when considering dosage forms or routes of administration for which the reference product is not authorized. Experience demonstrates that routes of administration (e.g., subcutaneous versus intravenous), and	Accepted

	even minor changes in the formulation of a dosage form, can be associated with differences in efficacy and safety, including the risk of immunogenic effects.	
	A detailed risk management plan must be developed for each investigational product. The plan must provide for evaluation of the potential for immunogenic effects before and after each similar biological medicinal product is marketed. It should include pre-approval evaluation in animal models and clinical trials, but also detailed information on how immunogenicity, and PRCA in particular, will be monitored in the post-marketing environment. Requirements for such testing may differ depending on the intended patient population; for example, the risk of immunogenic effects of erythropoietin may be greater in patients treated for chronic renal failure than in cancer patients. In establishing requirements for immunogenicity testing, patient safety must always be the primary consideration.	Accepted The applicant of a 'biosimilar' epoetin will have to submit a pharmacovigilance /risk management plan which will be evaluated by CHMP. Generally, the requirements will be based on the clinical safety experience for the reference product, the product class and the safety data obtained for the medicinal product for which marketing authorisation is sought. Traceability will be addressed in the general guideline.
	Because the immunogenic effects identified to date are rare, it will also be necessary to require formal programs of post-market surveillance. Ordinary pharmacovigilance procedures, which rely on spontaneous reports from health care professionals, will not be sufficient. Key elements will include accepted definitions for PRCA for post-marketing case assessment, detailed information for prescribers on how to evaluate loss of effect, and provision of antibody testing on request to diagnose antibody-mediated PRCA. It may also be necessary to carry out comparative clinical trials or epidemiological studies after products are authorized. A complete benefit/risk assessment for an innovative product cannot normally be made until 2-3 years after it enters the market, and this will most likely also be true for similar biological medicinal products. Companies that market such products must provide assurances that they will maintain adequate systems, procedures and personnel to carry out post-marketing surveillance programs on a long-term basis, post-marketing studies and other pharmacovigilance commitments. This requires being able to properly identify these products, with the use of a brand name. The safety section of the labeling of the product concerned should be harmonized with the labelingof the reference product and any safety information, which would be class-specific.	See comment above. The safety section of the labelling of the "biosimilar" product will include all class-specific safety information.
	After similar biological medicinal products enter the market, they should be subject to the same change-control requirements that apply to all biotechnology products. Attention must be given to all relevant matters (e.g., changes in the manufacturing process, finished product formulation, packaging and conditions of storage and distribution).	Accepted This is beyond the scope of the intended guidelines. However, once a MA has been granted the "biosimilar" product is a product on its own and the same change-control requirements will apply as for the innovator product according to relevant guidelines
	In view of the special issues regarding immunogenicity, potency and other factors, erythropoietin products developed under the procedure for similar biological medicinal products (like products that have been developed by innovative manufacturers) should not be treated as therapeutically interchangeable unless adequate clinical data support the	The issue of interchangeability is beyond the scope of the intended guideline. Traceability will be

	specific claim of interchangeability. This is particularly important to insure that post-marketing surveillance programs can be carried out effectively. If immunological events or other side effects occur in patients who have received multiple products, it will be difficult to determine which product was associated with those effects.	addressed in the general guideline.
	From a manufacturing perspective, phase III trials should be conducted with the final formulation	Accepted Addressed in the general guideline
1. **Paragraph 1,** **line 2:**	**2. Section-by-Section Comments** **Introduction** The draft refers to demonstration of "comparability" of the claimed-similar product to a reference product. The term "comparability" should be reserved for the type of evaluation contemplated by ICH Topic Q5E, which governs changes in the manufacturing process for an existing biological medicinal product from the same manufacturer. Such changes are evaluated in light of full information on the manufacturing process and specifications for the original product, which is not available to applicants seeking approval of similar biological medicinal products. It is more appropriate to state that the applicant is seeking to demonstrate that its product is "similar" to a reference product in terms of quality, safety and efficacy, and to recognize that the requirements for demonstrating similarity may be quite different from - and often more demanding than - those for demonstrating comparability. The manufacturer of a claimed-similar product must, of course, also comply with the requirements of ICH Topic Q5E in the same manner as the manufacturer of an innovative product -- that is, it must demonstrate internal comparability at each stage of the development process and throughout the post-approval life cycle of the product.	Not accepted We believe that by issuing separate guidelines for changes in the manufacturing process and for 'similar biological medicinal products', the difference is made clear. Nevertheless, a comparability exercise has to be performed to demonstrate the similar nature of two medicinal products.
Paragraph 4, **lines 3-4:**	The draft states that the "mechanism of action of epoetin is the same in all currently approved indications …." In fact, pharmacokinetics and pharmacodynamics are disease-dependent. It is therefore not appropriate to approve a product for multiple indications based on a single clinical trial in one indication. At a minimum, a comparative PK/PD study should be conducted in each indication to demonstrate that the claimed-similar product is equivalent to the reference product.	Not accepted. The basis for extrapolation to other indications is that the mechanism of action of the therapeutic protein is the same. Clinical equivalence trials should be performed in the most sensitive model, which is renal anaemia in case of epoetin.
Paragraph 5, **lines 3-5:**	The rate of hemoglobin increase is not only dependent on dose and the other factors identified, but on the dosing regimen.	Accepted
Paragraph 6	The statement "treated with subcutaneously administered epoeitin" could be misleading.	Will be reworded.
Paragraph 1:	**2. Scope** The draft should clearly state the requirements set forth in the Guidance are applicable only to epoetin products, and not to second-generation products such as darbepoetin.	Not accepted Although the annex addresses recombinant human erythropoietin, the general principles would also apply e.g. to darbepoetin.
Paragraph 1, **lines 3-4:**	The similar nature of two biological products should be demonstrated not only in terms of "safety and efficacy" but in terms of pharmacokinetics and pharmacodynamics.	Accepted. For this reason comparative PK and PD studies are required

Paragraph 2, lines 3-5:	The last sentence states that the final set of studies necessary to fulfill non-clinical and clinical requirements for a given medicinal product will be determined by data generated by the comparability exercise itself. Although we agree that additional tests may be required depending on the outcome of initial testing, there should be a clearly delineated core of studies required to demonstrate that a biological medicinal product is similar to a reference product, and these studies should always be demanded as a minimum.	Accepted. The annex states that at least two clinical trials are required
3.	**Non-clinical studies** The introduction states that non-clinical studies should be comparative in nature and should be designed to detect differences in response to the similar biological medicinal product and the reference product. If significant differences are detected in non-clinical studies, it will be inappropriate to permit a product's development to proceed under the procedure for similar biological medicinal products. Instead, the product should be developed as a new chemical entity, subject to a full and independent program of non-clinical and clinical testing. Even before non-clinical studies are conducted, there should be adequate demonstration that the claimed-similar product has the same structure as the reference product, including (among other things) a similar glycosylation pattern. Technical studies should be performed to identify the exact structure in terms of glycoprotein structure and glycosylation, with additional explorations to determine the extent of degradation of product in terms of dimers, aggregates, etc. and the impact of storage conditions. If significant differences are detected between the product under development and the reference product, use of the procedure for similar biological medicinal products is inappropriate.	Accepted
3.1	**Pharmacodynamics studies** ***In vitro studies*** Pharmacodynamic measurements should also include reticulocyte counts. ***In vivo studies*** This section should also require comparative single-dose and multiple-dose pharmacokinetic and pharmacodynamic studies in at least one relevant species.	Not accepted Reticulocyte counts Reticulocyte counts are typically measured in *in vivo* studies. In vivo PD and PK studies The NfG recommends comparative evaluation of the erythrogenic effects of similar biological medicinal product and reference medicinal product in an appropriate animal model, like e.g. the polycythaemic and/or normocythaemic mouse assay. Since pharmaco(toxico)kinetic information is obtained from the repeat dose toxicity study, separate single- or multiple-dose pharmacokinetic studies are not considered necessary.
3.2 *1st paragraph:*	non-clinical toxicology studies will never be adequate to reliably detect differences in immune response between the biosimilar and the reference product with sufficient certainty. Nevertheless, such studies are necessary to get preliminary information on significant differences concerning immunogenicity which might be relevant for the design	Partly accepted It is agreed that immune response in the

	of the following clinical studies. Thus, the last paragraph should read "... special emphasis should be laid on the preliminary determination of immunogenic responses".	repeat dose toxicity study (RDTS) is not predictive for immune response in humans. However, since the mmunological mechanisms are expected to be sensitive to potential structural differences between similar biological medicinal product and reference medicinal product, evaluation of immune response will contribute information to the non-clinical comparability exercise. Furthermore, determination of (neutralizing) antibody formation constitutes an essential component of the toxicokinetic evaluation and is e.g. required to estimate the exposure of animals to ´free` erythropoietin during the RDTS.
4. **4.1**	**Clinical studies** **Pharmacokinetic studies** Equivalence should be demonstrated on the basis of AUC and Cmax. The default acceptance limits for the 90% confidence interval of treatment ratios should be 0.800 01.250 unless justified in advance on clinical grounds and agreed with the competent authorities. If these acceptance limits are not met, the applicant must demonstrate, through appropriate safety and efficacy studies, that the claimed-similar product can be administered in the same dosing regimen as the reference product in all claimed indications. If this cannot be done, the competent authority should consider requiring that the product be the subject of a full, independent development program, in the same manner as a new entity.	Accepted Generally agreed upon. However, the acceptance range of 0.80 to 1.25 has been established for essentially similar products but cannot necessarily be applied to similar biological medicinal products. A predefined and justified equivalence margin will have to be presented by the applicant. We acknowledge that this may be difficult until further experience is gained with 'biosimilar' applications.
4.2	**Pharmacodynamic studies** According to the draft Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (EMEA/CHMP/42832/2005), a pharmacodyamic marker should be selected on the basis of relevance to the therapeutic efficacy of the product. Under this principle, red blood cell counts and hemoglobin should be included in this section, in addition to reticulocyte counts.	Accepted Reticulocyte count is considered the most relevant and earliest measurable PD marker in a single dose study
4.3	**Clinical efficacy studies** This section seems to assume that all comparative efficacy studies will ordinarily be conducted in patients with renal anemia, on the theory that this is the most "sensitive" model. There are differences in patient responses, which are	Not accepted The mechanism of action involved in epoetin-stimulated erythropoeisis is not disease-specific. Therefore,

	disease-dependent, as well as pharmacokinetic and pharmacodynamic differences. Thus, extrapolation of efficacy and safety from these studies may not be appropriate, and at least needs to be carefully considered, particularly in the context of patient safety. We would recommend that each indication be considered separately in the guidelines. This will allow identifying the risks associated with each indication, and defining the need for investigation in order to address any potential safety concerns. Extrapolating efficacy and safety from renal failure to oncology where higher doses are used can be of concern regarding patient safety, with the potential for high responses at previously untested doses (e.g. increased hemoglobin levels exceeding recommended thresholds, both of which known to be associated with safety issues). These doses used in the oncology setting should be evaluated prior to approval, rather than as part of the pharmacovigilance plan. In fact, their testing should be part of an overall risk management strategy, including pharmacovigilance in the post-authorisation phase. Studies should examine the variability of response that may be due to variability in manufacturing or biological response. With repeated maintenance doses, the claimed-similar product should give as consistent a response as the	demonstration of therapeutic equivalence in the most sensitive model may allow extrapolation to the other indications of the reference product. Most safety issues are related to exaggerated pharmacodynamic response (such as hypertension, access-related events) and can be adequately assessed in the proposed clinical trials. In addition, epoetin is titrated according to Hb response. Immunogenicity is best assessed in patients with renal anaemia, which is the suggested patient population. Additional safety data will be required post-marketing.
4.3	Furthermore, the guideline should provide more detail on the equivalence margins that would be considered to be acceptable in the proposed studies. There is considerable experience with the reference products that has been generated over a number of years and it is entirely possible to define these margins in the guideline and thus ensure consistency in therapeutic efficacy amongst biosimilar erythropoietin products.reference product.	Not accepted. Different endpoints may be possible to demonstrate efficacy. Equivalence margins for these endpoints have to be presented and justified by the applicant taking into account the data generated with the reference product (and other epoetins if appropriate).
4.3	Dose adjustment algorithms should be identical to those of the reference product.	Accepted Is self-evident in an equivalence trial.
4.3	Transfusion requirement should be a primary, rather than secondary, endpoint, because it represents the ultimate clinical benefit.	Not accepted While this could be an appropriate primary endpoint to demonstrate clinical benefit e.g. in a new indication, it is not sensitive enough for demonstration of comparable efficacy of two epoetins.
4.3. 6th paragraph:	A paragraph should be added pointing out that patients which were treated with different erythropoietin brands (or a brand distinct from the reference product) should not be included in any clinical programme with the similar biological medicinal product concerned.	See comment above
4.3, 9th paragraph:	The last sentence should read "... any relevant difference in the used dose (lower or higher) would contradict the assumption of similarity" since these studies have to be designed to prove similarity, and not "non-inferiority" (i.e., superiority of the assumed biosimilar, as compared to the reference product, would be not acceptable for proof of	Accepted However, the guidance documents already state several times that

	similarity – a "better" outcome is no option).	equivalence is needed and that equivalence margins have to be pre-defined and justified.
4.3, 12th paragraph:	"Therapeutic equivalence" requires Pharmaceutical Equivalence (including proof of identity of active pharmaceutical ingredients (API), plus Bioequivalence (Ref. presentation of H.-Y. Ahn at the DIA-FDA Workshop on Follow-on Protein Pharmaceuticals, 2005). It is generally accepted – also in the EU regulations and CHMP draft guidelines - that "identity" of API can not be shown for a biosimilar as compared to an innovator protein manufactured by a different process (basis for defining "Biosimilars" instead of "Biogenerics"). Thus, a biosimilar can *never* be "therapeutically equivalent" to an innovator protein drug. Therefore, the first sentence should be replaced by "**Similar therapeutic efficacy** has to be demonstrated...".	Not accepted Therapeutic equivalence does not imply (pharmaceutical) identity. It just means that efficacy is neither inferior nor superior. This is important in order to adopt the posology of the reference product.
	The guideline should specify that non-inferiority or equivalence testing is at the 2.5% level not as still recommended for bio equivalence trials at the 5% level.	Not accepted The guideline clearly states that "equivalence trials" will be required and makes reference to Guideline ICH E9 and E10. Additional useful references regarding statistical principles may be included. However, we believe that general principles in the conduct of equivalence trials outlined in specific guidelines should not be repeated in this product-specific annex
5.	**Clinical safety** Safety data should be required for each indication. Experience suggests that there can be significant differences in side effect profiles in different patient populations, and the safety of the claimed-similar product must therefore be evaluated in each indication. This is confirmed by the summaries of product characteristics for epoetin products authorized in the EC -- section 4.8 of the SmPC ("undesirable effects") contains separate entries for renal, cancer and surgical indications, and the adverse events identified in those sections are substantially different. For renal indications, for which patients often receive erythropoietin for several years, safety studies should include at least 300 patients who undergo actual treatment for at least 12 months. For oncology indications, treatment is usually for only 12-16 weeks, but long-term follow-up (1-2 years) may be required to assess effects on tumor proliferation and survival. For surgery indications, in which patients are normally treated for 3-4 weeks, studies of significantly shorter duration may be appropriate. Safety with 300 patients is insufficient as there is e.g. a too high likelihood to see only 0 or 1 immunogenicity event, although the rate is fairly high, e.g. above 1%. For an adverse event that occurs in 5% of patients, the current proposal of 300 patients allows exclusion of only an approximately 3-fold increase in risk.	Not accepted Most adverse reactions are related to exaggerated pharmacodynamic response (such as hypertension, access-related events). Common events can be adequately assessed in the proposed clinical trials. In addition. epoetin is titrated according to Hb response. Immunogenicity is best assessed in patients with renal anaemia, which is the suggested patient population. The guideline will not state a specific number of patients to be assessed for immunogenicity (see comment above). Additional safety data will be required post-marketing.
	It is important to recognize that heightened efficacy may present safety problems in some patient populations. For example, enhanced hematopoietic effect may increase the risk of thrombosis. Thus, any significant increase in	Accepted Therefore, demonstration of equivalent

	efficacy observed in comparative efficacy trials must be carefully evaluated for its safety implications.	efficacy rather than non-inferiority is required.
	Determination of immunogenicity requires a balance of pre-approval and post-authorization studies, with attention to the route of administration, duration of therapy and choice of patients. Immunogenicity is best demonstrated in patients with chronic renal failure who are naïve to therapies with erythroploietic products and who will receive at least 12 months of chronic therapy by the subcutaneous route. Antibody screening of asymptomatic patients in pre-approval studies should be performed with the understanding that it can only detect a very high rate of immunogenicity and will not be adequate to detect rare events, such as pure red cell aplasia. The asymptomatic presence of low-affinity non-neutralizing antibodies to erythropoietin has not been shown to be predictive of which patients will develop PRCA. For detection of erythropoietin antibodies, a standardized, validated, highly selective assay should be used that is acceptable to health authorities.	Accepted. Addressed in guidance document.
	Retention samples for both "titration" and "maintenance" studies are recommended to allow examination of batches for variability and quality that will be useful for investigation should immunogenicity occur. Additional technical explorations should determine the impact of storage conditions and aging on the extent of degradation or products (in terms of dimers, aggregates, oxidation, etc.).	Accepted. Retentions samples are recommended in the guideline.
5., 2nd paragraph:	It should be stressed that assays used for testing antibody formation have to be specific for the biosimilar protein itself. Thus, "generic" assays (or assays developped for the reference compound) may not be adequate. Specificity/selectivity and sensitivity of the assays have to be demonstrated and validated. Thus, the last sentence should read "For detection of anti-epoetin antibodies, a validated, highly sensitive assay, which has been demonstrated to be specific for the biosimilar product should be used". Commercial assays will usually not be adequate.	Not accepted It is unclear why different antibody assays would be necessary for two similar epoetins.
	Safety information, which is class-related or specific to the reference product should be considered in the labeling of a similar biological medicinal product.	Accepted
6.	**Pharmacovigilance plan** The sponsor must present a pharmacovigilance plan and a program of post-marketing clinical studies to address immunogenicity and potential rare serious adverse events. Special attention should be paid to the possibility of erythropoietin antibody-induced PRCA and immune-related adverse events. The risk management plan developed should include (1) appropriate guidance in the label; (2) proactive pharmacovigilance (case ascertainment, formation of an independent safety advisory committee, aggregate data assessment, long-term case follow-up, prospective exposure monitoring and a decision strategy for spontaneous reports); (3) educational programs; (4) a post-approval immunogenicity surveillance registry; and (5) a process for re-evaluation of the risk management plan.	The requirements for the pharmacovigilance /risk management plan will be based on the clinical safety experience for the reference product, the product class and the safety data obtained for the medicinal product for which marketing authorisation is sought. Requirements and considerations are addressed in the general guideline and in the.product-specific annexes
	We recommend that the language in section 6 be revised to read as follows: "Within the authorization procedure the applicant should present a pharmacovigilance plan/risk management program in accordance with current EU legislation and pharmacovigilance guidelines (ICH Topic E2E). This should take into account risks identified during product development and potential risks, especially as regards immunogenicity and	Comment will be taken into account.

	potential rare serious suspected adverse reactions such as pure red cell aplasia, and should state in detail how these issues will be addressed in post-marketing follow-up. Monitoring of antibodies should be followed in the post-marketing setting with a well-validated anti-epo assay. Such monitoring should be conducted on the basis of a protocol designed to ensure that a sufficient number of patients are followed for a long enough period to detect rare but serious immunological events."	
	Higher doses used in different indications (e.g. oncology) should be tested before authorisation of the product. This element should be part of an overall risk management strategy, complemented by pharmacovigilance in the post-authorisation phase.	Partially accepted Regrding extrapolation of indication see comment above. Post-marketing safety data should be collected from a cohort of patients representing all approved therapeutic indications.
6., 1st paragraph:	CHMP rightly requests a pharmacovigilance plan for the post-approval phase. It should be added that this requires branding of the biosimilar product because compound-specific monitoring would not be possible if (possibly several) biosimilars are marketed under a generic name/INN	Not accepted Beyond the scope of the guidance document.
7.	**Extension of indication** As noted above, each major indication (renal, oncology, surgical use, etc.) and each dosing regimen for such an indication must be supported by comparative pharmacokinetic and pharmacodynamic studies and comparative clinical studies of safety and efficacy. Efficacy studies may have different end points depending on the nature of the condition that is treated.	Not accepted Extension to other indications of the reference product may be possible (see comment above).
	Annex **<u>Points to consider regarding immunogenicity</u>** Immunogenicity is the property of a substance to provoke an immune response when brought into a human or animal organism. This includes the formation of antibodies and may result in the development of immunity, hypersensitivity, or tolerance.	Agreed
	Monitoring immunogenicity in clinical trials Because of the lack of predictive and validated preclinical methods for the assessment of immunogenicity, only clinical trials are decisive to reveal immunogenicity. The correlation between antibody formation and pharmacokinetics or pharmacodynamics has to be evaluated concerning their relevance for efficacy and safety. In most cases, the risk of immunogenicity will have to be considered in different therapeutic indications separately. A comparison of immunogenicity of innovative and biosimilar protein products can only be made in comparative clinical trials. Therefore, in the interest of patient safety, no protein drug should be approved without data on its immunogenic properties obtained in clinical studies of adequate size and duration (e.g., in the case of chronic administration, one-year follow-up data will be required). The patients' immune system may be influenced by the disease as well as by co-medication; this may lead to the observation that the incidence and clinical phenotype is different for the same product when used in different indications.	Accepted At least 1-year immunogenicity data will be required pre-approval in the patient population with the highest risk, i.e. patients with renal anaemia.

	During these studies, the formation of anti-product antibodies has to be analyzed carefully with sensitive and compound-specific **validated assays**, e.g. enzyme immunoassays, and their correlation with clinical findings has to be investigated. The timely availability of these assays to monitor, confirm and characterize immunogenicity in clinical studies is a prerequisite for any clinical program. ELISA-based assays are considered to be state-of-the-art for screening purpose. They should be designed in an appropriate way to be able to detect low-titer and low-affinity antibodies. If antibody formation is observed and confirmed by additional assays, the antibodies have to be characterized carefully in order to assess the impact on the therapy scheme, patient selection, etc. Usually functional assays with the capacity to detect neutralizing effects of the anti-product antibodies need to be available. The nature of these functional assays will depend on the actual drug and the type of drug target intervention. In any case they have to be developed separately for each product.	Accepted Validated and sensitive assays are required in the guidance document. Antibodies, if present, will need to be characterized.
	Need of post-approval risk management Because there is considerable inter-individual variability in antibody response, current regulatory guidelines request data to be collected from a sufficient number of patients to characterize the variability in antibody response. Rare immunogenic events, e.g. the PRCA case, will not be detectable in pre-approval clinical trials due to the lack of sufficient patient numbers which would be required for adequate statistical evaluation. Therefore, for any therapeutic protein (including biosimilars), a post-approval surveillance program will be necessary which includes immunogenicity testing, pharmacovigilance and relevant epidemiological data. In order to achieve this goal, any biosimilar must be identifiable, i.e. a brand name must be used, and substitution cannot be an acceptable practice.	Partially accepted The applicant will have to submit a pharmacovigilance / risk management plan that will be evaluated by CHMP (see comment above). Traceability is addressed in the general guideline. The issue of interchangeability is beyond the scope of the guideline.
	How similar can / must Biosimilars be? We fear a serious risk of under- or overdosing patients and toxicity issues.	Similar biological medicinal products will need to show comparable efficacy and safety. An equivalence margin for efficacy is chosen by defining the largest difference that is clinically acceptable (i.e clinically not relevant). This will ensure that patients are not under- or overdosed with the 'biosimilar' product.
	Are all patient factors identified? What with unknown patient factors? What about the risk of side effects and / or drug efficacy?	There is ample experience with the use of epoetins in the approved indications. Unknown patient risk factors would constitute a risk not only for the 'biosimilar' but also for the reference product. Clinical trials are necessary to demonstrate comparable efficacy and safety of the 'biosimilar' epoetin and the reference product.
	We question, if it is enough to basically provide principles? Are the required non-clinical and clinical data sufficient	A full quality dossier will have to be provided. In addition, a thorough comparability exercise in terms of

		quality, safety and efficacy will have to be performed. This is not trivial and much more than providing "principles". On the other hand, it is not the intention of the guideline to give an exact recipe of how to develop a "biosimilar" medicinal product.
	In our view, also post-marketing risk management programmes must be a part of the marketing authorisation procedure. This includes updated safety reports.	Accepted. Required by legislation and addressed in the guideline.
1st paragraph	Introduction We would recommend to add a reference to Directive 2001/83/EC as done for the overarching *Guideline on biosimilar medicinal products.* The legal basis for this guideline is Article 10(1)(a)(iii) of Directive 2001/83/EC, as amended, Part II of the Annex I of Directive 2001/83/EC, as amended, which lay down the requirements for the Marketing Authorisation Applications (MAA) based on the demonstration of the similar nature of the two biological medicinal products. According to this legal document we would recommend to amend the introductory statement to bring it in line with the community code for pharmaceutical products.	Not accepted. This is a product-specific annex to the general guideline which should not repeat general information.
	A company may choose to develop a new biological medicinal product claimed to be similar (similar biological medicinal product) in terms of quality, safety and efficacy to an original/reference product that **is or has been authorized** ~~has been granted a marketing authorisation~~ in the Community (see Guideline an similar biological medicinal products, CHMP/437/04).	Not accepted Wording of the general guideline (for 'biotech products') is used in the annex.
1st paragraph	Non-clinical studies Pharmacodynamics studies *In vitro studies* In order to obtain reliable results for biological activity within the scope of a sound development programme for biosimilars, we recommend to use only validated comparative bioassays. We suggest a slight amendment of the paragraph. In order to assess any alterations in reactivity between the similar biological medicinal product and the reference medicinal product, data from a number of **validated** comparative bioassays (e.g. receptor-binding studies, cell proliferation assays), many of which may already be available from quality-related bioassays, should be provided.	Partly accepted Of course, the use of validated assays is supported. However, concerning the non-clinical comparability exercise, relevant information may also be derived from *in vitro* assays not formally validated, taking into account the principle that the applied studies should be designed to detect differences in the response between similar biological medicinal product and reference medicinal product rather than the response *per se*.

1st paragraph, last sentence	Toxicological studies In Chapter 6 Immunogenicity – Principles for evaluation of immunogenicity of the *Guideline on similar biotechnological products: non-clinical and clinical issues (EMEA/CHMP/42832/2005)*: it is stated "*Normally an antibody response in humans cannot be predicted from animal studies*". Therefore, it is not clear why this paragraph under consideration puts such a strong emphasis on immunogenicity testing. The CHMP should either add a rationale explaining why preclinical immunogenicity testing is relevant and required, or outline in this section of the guideline that antigenicity in non-clinical model systems is typically not predictive for antigenicity in humans. Accordingly we propose the following change. ~~*In this context, special emphasis should be laid on the determination of immunogenic responses.*~~*F***or evaluation of immunogenicity it should be noted, that most of the biological products are species specific. Therefore, immunogenicity has to be interpreted as a consequence of exposure to foreign protein. It has to be noted that this kind of immunogenicity observed in non-human systems should always be interpreted as being dependent on the test-system but not related to the substance under investigation**.	Partly accepted It is agreed that immune response in the repeat dose toxicity study (RDTS) is not predictive for immune response in humans since it largely reflects consequences of application of a ´foreign` protein to an experimental animal. However, since the immunological mechanisms are also expected to be sensitive to potential structural differences between similar biological medicinal product (SBMP) and reference medicinal product (RMP), determination of immune response in the RDTS will provide additional information about non-clinical comparability of SBMP and RMP. Furthermore, determination of (neutralizing) antibody formation constitutes an essential component of the toxicokinetic evaluation and is e.g. required to estimate the exposure of animals to ´free` erythropoietin during the RDTS.
3rd paragraph	Toxicological studies For completeness of this paragraph, the toxicology programme described in the paragraph we recommend to add teratogenicity to the list of not-required studies. Safety pharmacology, reproduction toxicology, **teratogenicity**, mutagenicity and carcinogenicity studies are not routine requirements for non-clinical testing of similar biological medicinal products containing recombinant human erythropoietin as active substance.	Not accepted Since, per definition. teratogenicity studies are a part of the ´reproduction toxicology studies`, they do not need to be listed separately.
1st paragraph, 1st sentence	Clinical studies Pharmacokinetic studies	Not accepted. Single dose PK studies are considered sufficient to detect possible differences in the PK profile between the 'similar' and the reference product. Since

	We agree that the pharmacokinetics of the biosimilar medicinal product and the reference product may be investigated in single dose studies. However, depending on the overall clinical development design, a multiple dose study may be more suitable and provide more relevant information than a single dose study. Therefore, the scope of this section should be extended to also include multiple dose studies. *The relative pharmacokinetic properties of the similar biological medicinal product and the reference product should be determined in single **or multiple** dose crossover studies using subcutaneous and intravenous administration.*	clinical trials are obligatory, multiple dose studies are not needed.
1st paragraph, 2nd sentence	We propose to amend the sentence slightly in order to make clear that the equivalence margins must be defined in writing before commencement of the study. Healthy volunteers are considered an appropriate study population. The primary PK parameter is AUC and the secondary PK parameters are C_{max} and T1/2. Equivalence margins have to be defined a priori **in the study protocol** and justified, primarily on clinical grounds.	Not accepted This is self-evident.
Below 1st paragraph	For biosimilar medicinal products containing recombinant human erythropoietin a separate investigation of pharmacokinetics for either route of administration (intravenous or subcutaneous) is recommended. This requirement is based on the fact that the pharmacokinetics profiles for the i.v. and s.c. administration are different. Therefore, we recommend to add a note to this section. *If different routes of administration (e.g. subcutaneous and intravenous) with distinct pharmacokinetic profiles are claimed, PK studies have to be performed for each route of administration.*	Not accepted For epoetins it is known that the PK profiles for SC and IV administration differ.
1st paragraph, 1st sentence	<u>Pharmacodynamic studies</u> Depending on the overall development concept, one comparative PD study may be sufficient for demonstration of equivalence. We recommend to rephrase the sentence slightly to be more precise. Reticulocyte count is a relevant pharmacodynamic marker for the activity of epoetin and recommended to be used in **at least one** comparative **single dose** pharmacodynamic stud~~ies~~. On the other hand, reticulocyte count is not an established surrogate marker for efficacy of epoetin and therefore no suitable endpoint in clinical trials.	Not accepted Since the PK profiles differ for the SC and IV route of administration, PD parameter should also be assessed for both routes. PD is best assessed within the two PK studies. This will be clarified in the annex.
Below 1st paragraph,	Measurements of reticulocytes are only reasonable in single-dose studies because they are no accepted surrogate parameter. However if haemoglobin is used for assessment of the pharmacodynamic response, also multi-dose studies may provide valuable results as comparable changes in haemoglobin can be assessed in volunteers as in patients.. **Besides reticulocyte count changes a haemoglobin response can be assessed in healthy volunteers after multiple dosing. As hemoglobin is a valid endpoint in clinical trials it is a accepted surrogate marker for efficacy of epoetin. Therefore multiple dose PD studies measuring the change in haemoglobin may be used for assessment of therapeutic equivanlence if the equivalence margins are justified on clinical grounds.**	Not accepted PD studies will not suffice to demonstrate therapeutic equivalence. Clinical trials will be necessary to demonstrate comparable efficacy and safety.

	Clinical efficacy studies **1st paragraph** The original suggestions to conduct to separate studies for investigation of the effects of epoetin in pre-dialysis and dialysis patients is not based on scientific grounds. According to the *revised European best practice guideline for the management of anaemia with chronic renal failure* (Locatelli et al, 2004) pre-dialysis and dialysis patients with an haemoglobin level below 11 g/dl should be treated with the same therapy. In both patient population the mode of action is the same and also the posology during the titration phase is identical. Further, the doses applied will vary significantly between the individual patients but only minimally between the two indication groups. Based on this scientific basis we would recommend to revise the paragraph accordingly Equivalent therapeutic efficacy between the similar and the reference product should be demonstrated in at least ~~two~~ **one** adequately powered, randomised, parallel group clinical trials.	Partially accepted Similar efficacy and safety of the 'similar' and the reference medicinal product should be shown for the titration phase and the maintenance phase as well as for different routes of administration. The focus of the titration phase study is on response dynamics and related adverse events. The maintenance phase study is more sensitive to show differences in efficacy. Since dosages differ for IV and SC use, both routes of administration have to be investigated separately. Therefore, a minimum of two clinical trials is necessary for demonstration of similar efficacy and safety. We agree that it is not necessary to demonstrate efficacy and safety in both haemodialysis and pre-dialysis patients. The study proposals (Note: only a proposal, no requirement) were made because epoetin therapy is usually started SC in the pre-dialysis phase of chronic renal insufficiency whereas the IV use should only be considered in patients on haemodialysis. Therefore, pre-dialysis patients are considered the appropriate patients to be included in the titration phase study and haemodialysis patients in the maintenance phase study. Because of different dose requirements pre-dialysis and haemodialysis patients should not be mixed in the same study. The concerned paragraph will be reworded to clarify the issue.
4th paragraph	In line with our comment above, we do not recognize scientific grounds supporting the requirement for two	Not accepted

	independent studies. Therefore, we suggest to amend the paragraph accordingly. The clinical trials~~s~~ **programme** should **either** include a `titration phase' study during anaemia correction and**/or** a `maintenance phase' study in patients on epoetin maintenance therapy.	See comment above
6th paragraph, 1st sentence	We propose a slight amendment in order to make the sentence more precise and be consistent with the wording of other paragraphs above. The study design for a maintenance **phase** study should minimise baseline heterogeneity and carry over effect of previous treatments.	Comment will be considered.
6th paragraph, 2nd sentence	If patients are optimally titrated prior to randomization into either of the two arms, there are sufficient scientific grounds to presume that a two-month base-line period instead of three months is sufficient. Further, we recommend slight changes in order to use a consistent and more precise wording. It is recommended to include in a maintenance **phase** study patients optimally titrated on the reference product (stable haemoglobin in the target range and stable epoetin dose and regimen) for at least **two** ~~three~~ months. Thereafter, study subjects should be randomised to the similar or to the reference product **keeping the same dosage** and followed up for of at least three month. A longer period **of the** comparative phase (e.g. 6 months) will be needed if baseline treatment heterogeneity and carry over effects cannot be excluded.	Not accepted See comment above
8th paragraph, 1st and 2nd sentence	We recommend some rephrasing of this paragraph in order to make it better understandable and consistent with the previous text. In the course of these studies, epoetin doses should be closely titrated to achieve **therapeutic levels of hemoglobin (titration phase study) or** ~~and~~ maintain **therapeutic** haemoglobin concentrations **(maintenance phase study**). The protocol should clearly pre-define ~~the haemoglobin changes~~ **a therapeutic window for haemoglobin and dosage regimen changes if dose adjustments are necessary to keep the patient in the therapeutic window for haemoglobin** ~~that will demand a change in the dose of epoetin.~~	Partially accepted The concerned paragraph will be partially reworded.
8th paragraph, 3rd sentence	The suggested amendments to this paragraph are based on the clinical study design for the pivotal trials conducted for the authorization of darbepoetin. In these studies the endpoint was the change of haemoglobin upon treatment with erythropoietin analogue. Further, according to the scientific literature the haemoglobin concentration is the typical endpoint in titration or maintenance phase studies (EPAR Darbepoetin CPMP/1299/01; Nissenson *et al.* American Journal of Kidney Diseases, Vol. 40, no1, 2002, page 110-118). Therefore, it should also be considered a valid endpoint. Preferably, `haemoglobin responder rate', i.e. proportion of patients achieving a pre-specified haemoglobin target in the `titration phase study' or ~~haemoglobin maintenance rate' (~~proportion of patients maintaining haemoglobin levels within a pre-specified range in the `maintenance phase study **should be considered as the primary endpoint. Alternatively, mean changes in the haemoglobin concentrations between screening/baseline and end of study can be considered and be compared between different treatment groups with respect to a pre-specified limit in**	Accepted Responder rate as well as mean change in Hb has been used as primary endpoint in clinical trials. This will be reflected in the annex.

	the maintenance phase study. ~~and epoetin dosage should be co-primary endpoints~~. **The combination of a stable hemoglobin level and a stable epoetin dosage should be considered a major secondary endpoint in the maintenance phase study. For titration phase studies a major secondary endpoint should be the proportion of patients achieving the pre-specified hemoglobin target for a specific dosage level.**	
1st and 2nd paragraph	Clinical safety The duration of efficacy trials may differ between the various development programs for biosimilar recombinant erythropoietin products. By referring to the duration of the efficacy trials without providing a time period, the amount of safety data required is not precisely defined. Neither is the timepoint described at which the 12-month immunogenicity data have to be available. We therefore recommend to amend these paragraphs accordingly and define the exact amount of safety data as well as the timepoint of availability of the immunogenicity assessment.	Accepted More precise language will be used.
	Safety data from at least 300 patients treated with the similar biological medicinal product ***over 6 months*** ~~*in the efficacy trials*~~ *is considered sufficient to provide an adequate pre-marketing safety database and to exclude excessive immunogenicity.* The applicant should provide at least 12-month immunogenicity data in patients treated with the similar biological medicinal product **prelicensing**.	Not accepted Safety data from the clinical trials are considered sufficient to assess the safety profile pre-authorisation. With the exception of antibodies, adverse reactions develop early on. 12-month immunogenicity data should be provided pre-licensing.
Below 2nd paragraph	The exposure of cancer patients to epoetins is significantly different to that of patients with chronic renal failure (CRF). In CRF patients erythropoietin itself is the limiting factor, while in cancer patients the number of target cells responding to erythropoietin is very limited. In order to stimulate erythropoiesis CRF patients are treated with significantly lower concentrations of epoetin than cancer patients. CRF is a chronic disease requiring epoetin treatment until the end of the patient's life or until a kidney transplantation becomes feasible. In contrast, cancer patients receive epoetin to compensate the myelotoxic effects of chemotherapy on the haematopoietic system, which is a rather short time in comparison to chronic treatment. These major differences justify the requirement for a separate safety evaluation in cancer patients. If these oncological indication(s) are claimed with the initial marketing authorization application, the safety data should be available pre-licensing. ***For oncological indications, with typically higher epoetin doses, additional safety data in this patient collective should be generated pre-licensing.***	Not accepted Since most safety issues are related to exaggerated pharmacodynamic response and similar efficacy and safety will have to be demonstrated in the most sensitive model (renal anaemia), no additional safety data for oncology patients should be required pre-authorisation. In fact, oncology patients are the least sensitive model to detect differences in efficacy or safety. However, additional safety data, including all approved indications, will have to be generated post-marketing.
	Pharmacovigilance plan	Not accepted See comment above.

	2nd paragraph The safety data for indications with a safety profile expected to be different from that of CRF patients should be available pre-licensing. The sentence should therefore be moved to *Section 5 Clinical Safety* and slightly rephrased (see section above) ~~For those indications where higher epoetin doses are required additional safety data should be generated.~~	
	Regarding the PK studies, section 4.1, the guideline could benefit from an explicit definition of the acceptable equivalence margins. As it reads now, the guideline does not seem to consider the "conventional" 0.8 to 1.25 range for 90%CI around GMR of test/reference as generally appropriate. I believe that, for clarity, a certain specific definition of "equivalence" in this setting should be given – while a justification, based on clinical grounds, would be required for potential alternatives.	Not accepted. The acceptance range of 0.80 to 1.25 has been established for essentially similar products but cannot necessarily be applied to similar biological medicinal products. A predefined and justified equivalence margin will have to be presented by the applicant. More experience will be needed before definite equivalence margins can be set
	Regarding the "titration efficacy study", section 4.3, it might be useful to be more specific about the two co-primary outcomes. Since the "responder rate" is a proportion, it is rather obvious that a power calculation for the study would be based primarily on this outcome. On the other hand, as pointed out in the guideline, considering the mode of epoetin administration, i.e., titration of the dose according to the Hb response, it is plausible to assume that in any test vs. reference comparison the targeted "response" would be eventually achieved with both products – the focus then is moved towards epoetin utilization required for such a response. Under these conditions, it might be useful (to prevent uncertainties) to specifically define the outcome that would define the "dose". A variety of "definitions" is possible – cumulative dose over 12 weeks? Average weekly dose for the period spent in the trial? Average weekly dose for weeks 9-12? - that do not all provide the same kind of information. In my opinion, it might be useful, for simplicity and uniformity, to depict the preferred one. Also, it might be useful to explicitly advise that the equivalence of the "dose outcome" should be two-sided (+/-), while for the "responder outcome" non-inferiority would be appropriate (since, based on the overall clinical experience, the reference "responder rate" should be expected to be 90-95%). Regarding the "Hb maintenance study", section 4.3, it might be useful, just as above, to define the "dose outcome". However, in this setting the definition of "response" (and responder rate) is less obvious and potentially more important . To my understanding, the regulatory trials for NESPO and the trial that has brought the "once-a-week administration" approval for NeoRecormon used different definitions of this outcome, mainly in respect to the amount of change (drop) in Hb (vs. the "pre-evaluation period value") that was considered a "failure". Clearly, there are many possible "definitions" for this outcome. To define "success" or "failure" in keeping Hb at a certain level one could use different criteria: count patients in whom Hb has not dropped for more than 1 g/dL below the "entry Hb value" at any one week of the evaluation period (or for more than 0.5 g/dl?); or – for not more than 2 consecutive weeks? Or, for not more than any 4 weeks?; Determine an average deviation from the "entry Hb value" and then count patients for whom	Partially accepted. We agree that different endpoints may be possible to demonstrate efficacy. The most widely used in previous trials were. 'Hb responder rate' or 'mean change in Hb' for the Hb-targeted endpoint. These endpoints are recommended in the guidance document. The applicant will have to provide sound justification for the choice of endpoints and the pre-defined equivalence margins taking into account the data generated with the reference product (and other epoetins if appropriate). Equivalence margins are two-sided by definition.

	this average is not greater than -1 g/dl, or – 0.5?, etc. I am not sure that all these possible definitions give the same "type of information", nor that they would have identical repercussion on the dose requirement. In my opinion, it would be useful, for purposes of clarity and uniformity, to recommend a version that would be preferred.	
4.3.1	Suggestion: Alternative 1: Equivalent therapeutic efficacy between the similar and the reference product should be demonstrated in at least two adequately powered, randomized clinical trials. Alternative 2: Equivalent therapeutic efficacy between the similar and the reference product should be demonstrated in at least two adequately powered, randomized parallel group clinical trials, or if appropriate in a cross-over design, e.g. 'maintenance phase study'.	Cross-over studies are not favoured since they may hamper the assessment of immunogenicity.
4.3.2	Suggestion Alternative 1: Confirmatory studies should be double-blind to avoid bias. Alternative 2: Confirmatory studies should be double-blind to avoid bias, the use of double-dummy technique might be necessary to maintain double-blind conditions.	Double-dummy technique may not be acceptable from an ethical point of view since epoetin has to be injected
4.3.3	Suggestion: Therapeutic equivalence has to be demonstrated for both routes of administration, if both routes of administration are approved for the reference product in the most sensitive clinical model. This is best achieved by performing separate studies (e.g. when the reference product can be administered both via the i.v. and s.c. route a 'titration phase' s.c. study in a pre-dialysis population and a 'maintenance phase' i.v. study in a haemodialysis population)	Not accepted It is not intended to address the specific case of epoetin alfa in the guideline (also see comment above)
Chapter 5	Clinical Safety Suggestion: The applicant should provide at least 12-month immunogenicity data in patients treated with the similar biological medicinal product. 12-month immunogenicity data can be achieved by recorded administrations covering a 12-month period and a justified number of administrators (e.g. 100, scattered over 12 months).	Not accepted The current wording is considered very clear.
	It is not clear if the annex guideline will apply to any recombinant erythropoietin agent including Epoetin, Darbepoetin, and other potential innovative biologics where each one may independently be used as a reference product. It should be clarified whether a biosimilar product would have the option of demonstrating equivalent safety and efficacy to any of the marketed recombinant erythropoietin product that were approved on the basis of a full marketing application.	The principles laid down in the annex also apply to other than recombinant human erythropoietin
	Non-clinical data: The Concept Paper for erythropoietin (CHMP/146664/2004) indicated that recommendations would be given on the choice of the appropriate species and model to study safety pharmacology. The draft annex guideline contradicts the Concept paper and indicated that Safety Pharmacology studies will not be required.	Analysis of the non-clinical data available for recombinant erythropoietins revealed that safety pharmacology studies are not expected to add significant information to the non-clinical comparability exercise.
	Efficacy: No boundaries of definition for "therapeutic equivalence" are provided for the efficacy studies. Non-inferiority margins for demonstrating therapeutic equivalence should be clearly stated and should be as stringent as those required for the approval of a new biological entity or erythropoietin-stimulating agent.	Demonstration of therapeutic Equivalence rather than non-inferiority is required for a similar biological medicinal product. Regarding

	No range or guidance for "any relevant difference in the used dose" is provided, leaving the possibility for interpretation during the assessment period. Clear definitions for therapeutic equivalence including dose(s) are required a prior if common standards are to be applied across the review of potentially multiple applications for a single reference product.	equivalence margins see comment above.
	Clinical Safety: The scientific rationale for establishing the minimum number of patients at 300 for the evaluation of safety is not explained in the annex. Due to potential or actual differences in the manufacturing process, levels of impurities, stability and structural integrity between the biosimilar and reference product, a 300 patient safety database is insufficient to characterize therapeutic equivalence for the safety profile of a biosimilar erythropoietin product. The size of the safety data should be justified on the basis of the adverse event profile of the reference product and the ability to distinguish therapeutic equivalence of adverse events at the 0.5% to 5% level following months of therapy. Alternatively the biosimilar product should be expected to meet the requirements of ICH E1: The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions (total of 1500 patients exposure, at least 300 to 600 patients for 6 months, at least 100 patients for one year) The requirement for an adequately large safety database to characterize erythropoietins is demonstrated by the development of epoetin delta, darbepoetin alfa and epoetin beta, all of which are registered in the EU. Each of these products targeting the same receptor has determined a safety profile on the basis of exposure in approx 1300 to 1650 patients with at least 600 patients treated for 6 months and in excess of 150 patients treated for at least 1 year. A biosimilar product should not be held to a lesser standard.	The safety database from the efficacy trials are expected to be sufficiently large to provide an adequate pre-licensing safety profile of the "biosimilar" medicinal product. The exact antibody frequency of most epoetins (neutralising and non-neutralising) is not known and also depends on the sensitivity of the assay (the frequency of about 1% stated by Amgen is based on a highly sensitive assay). It is difficult to provide an exact estimate of the size of the required immunogenicity database. Therefore, the annex will not state a specific number.