European Medicines Agency

London, 22 March 2007
Doc. Ref. EMEA/CHMP/EWP/506296/2007

OVERVIEW OF COMMENTS ON GUIDELINE ON CLINICAL TRIALS WITH HAEMOPOIETIC GROWTH FACTORS FOR THE PROPHYLAXIS OF INFECTION FOLLOWING MYELOSUPPRESSIVE OR MYELOABLATIVE THERAPY (CPMP/EWP/555/95 Rev 1)

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

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	EFPIA	
2	Medicines Evaluation Board	Netherlands

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20)
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

GENERAL COMMENTS
1. The Note for Guidance is 'applicable to new biological products'. The modification of currently authorised haematopoietic growth factors rhuG-CSF and rhuGM-CSF through pegylation, is the main focus underlying the guidance of trials to be conducted . The benefit/risk issue and safety paragraph should receive more attention, as it may be that for other novel agents positive effects of a 'new biological product' (reduction the duration of neutropenia following myelotoxic chemotherapy), are counterbalanced by the adverse event profile. The replacement of haematopoietic growth factors could better be replaced by white blood cell growth factors. (see also point 2 below) 2. Comment: According to updated recommendation for 'the use of white blood cell growth factors' (J Clin Oncol July 1, 2006, published ahead of print), primary prophylaxis of febrile neutropenia (FN) is recommended in patients who have a high risk of F) based on age, medical history, disease characteristics and myelotoxicity of the chemotherapy regimen. Clinical trial data support the use of CSF when the risk of FN is in the range of 20% or higher. This is in agreement with the proposed guidance document. The rhuG-CSF although recommended, is used in the EU much less frequently as primary prophylaxis.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE: 1. INTRODUCTION

Line No and paragraph	Comment and Rationale	Proposed change (if applicable)
	It should be stated succinctly that this guidance applies to (1) biosimilar products and (2) new biological compounds including bioengineered biologics. The information is buried in this section; however, the languages like "One particular important purpose of this note for guidance …."and "The following guidance is applicable to new biological products. However, …" require readers to deduce the information.	'The following guidance is applicable to new biological products, <u>including bioengineered biologics, and biosimilars'</u>. ***Rapporteur's Comment*** *Accepted*
Para 1 Sentence 1	The term "haematopoietic growth factors that act on the myeloid lineage" is somewhat complex and inconsistent with current	Use "colony stimulating factors" or "granulocyte-colony stimulating factors" for greater specificity and consistency with current clinical

	pervasive usage of the term "[granulocyte-] colony stimulating factors", or "[G-]CSF". The abbreviation of "HGF" commonly used throughout the draft document does not maintain the specificity of myeloid lineage ("HGF" may refer to factors stimulating the erythroid or platelet cell lines). The latest internationally recognized clinical guidelines from (1) European Organization for Research and Treatment of Cancer (EORTC) "EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours." *European Journal of Cancer*, 31 May 2006, and (2) American Society for Clinical Oncology "2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline", *Journal of Clinical Oncology*, 01 Jul 2006, use similar "CSF" terminology. Finally, the earlier EMEA guideline EMEA/CHMP/BMWP/31329/2005, referenced as relevant in section 1 of this draft, also uses the term "granulocyte-colony stimulating factors"	terminology ***Rapporteur's Comment*** *Accepted.* *The term "colony stimulating factors" is more appropriate as there is a separate guideline for G-CSF, whereas this is a general guideline which may include other novel haemopoietic growth factors*
Para 5	Please clarify what is considered "new biological products." The sentence "The following guidance is applicable to new biological products. However, …." seems to suggest that bioengineered (eg pegylation) products are not considered new biological products. Also, only pegylated products are mentioned in this guidance; however, here are different ways to bioengineer proteins and they should also be considered.	Please also consider other types of bioengineered proteins ***Rapporteur's Comment***. *Accepted. The guideline now also refers to other bioengineered proteins*

Para 5 Sentence 6	In this guidance, the PK/PD methodology introduced is very generic (dose escalation design, estimating PK parameters, and establishing PK/PD relationship). Therefore, it is not clear why PK/PD methodology needs to be modified for pegylated proteins. Please clarify. The two sentences before the last sentence of this paragraph are quite confusing and would suggest them to be deleted.	Please clarify in what aspects that the PK/PD methodology is not appropriate to evaluate bioengineered proteins. ***Rapporteur's Comment*** *Accepted* *Following comments regarding section 8, the section on pegylation does not focus on pegylation alone but also refers to other bioengineered proteins. Accordingly, reference to PK/PD methodology for pegylated products alone has been omitted, only referring to changes in trial methodology. Sentences specified have been deleted.*
Page 3/10	The last paragraph . *The following guidance is applicable to new biological products. <u>However</u>, developments in the modification of <u>these</u> haematopoietic growth factors proteins through pegylation should be adapted*. The word 'however' and 'these' are not appropriate in this context	***Rapporteur's Comment*** *Accepted . The words "however" and "these" have been deleted*
	The words 'consequent impact on improved quality of life, compliance and cost effectiveness' should either be softened or deleted.	***Rapporteur's Comment*** *Accepted. The words 'consequent impact on improved quality of life, compliance and cost effectiveness' have been deleted.*

GUIDELINE SECTION TITLE: 2. PHARMACODYNAMICS – 3 PHARMACOKINETICS		

	Since the PD and PK endpoint can be collected from the same pharmacology studies, this guidance should encourage sponsors to collect both pieces of information from the same study; this way it could eliminate inter-study variability and better characterize the PK/PD relationship.
	
	Immunogenicty data should also be collected from human pharmacology studies
	
	The information in section2 3.1 and 3.2 should be introduced earlier when human pharmacology study is first mentioned (section 2).
		Please combine sections 2 and 3 into one section "Human Pharmacology Trials"
		• Study design – single and/or repeated dose escalation
		• Patient population
		  o Healthy volunteers
		  o Cancer patients
		• Assay Methodology
		  o PK
		  o PD
		  o Antibody
		• Data Analysis
		  o PK and/or PD parameters
		  o PK/PD relationship
		Rapporteur's Comment
		Accepted, sections 2 and 3 have now been combined and immunogenicity data has been included with a recommendation to collect PK/PD data from the same study to minimise inter-study variability.,

2.1 Pharmacodynamics	Effects on the blood cells (last sentence on page 3/10) should be specified. (please specify).	***Rapporteur's Comment*** *Accepted. Amended as shown below:* *"Side effects to be expected, as well as effects on the ~~blood~~ myeloid and non-myeloid cells including monocytes, lymphocytes, platelets and erythroid cells should be described.*

Page 4/10	The words ‘cytokine network’ are too aspecific and can better be avoided.	***Rapporteur’s Comment*** *Accepted. Amended as shown below* *“When trials in healthy volunteers are feasible, efforts should be directed at studying the effects of the new CSF on ~~the~~ other cytokines.~~network~~*

3.1 Pharmacokinetics	The sentence *'In addition, as repeated dosing with an HGF ….. higher dose levels'* is not well understood. It should be noted that donors treated with rhu G-CSF experience splenic enlargement and, rarely, spontaneous rupture of the spleen. The potential risks of marked leukocytosis (arbitrarily defined as a leukocyte count of more than 70×10^9/L) have been a concern, and rhG-CSF dose reduction is performed by many centers to maintain leukocyte counts below this level.	***Rapporteur's Comment*** *Accepted* *Sentence modified to include leucocyte count* *"In addition, repeated dosing with a CSF in healthy volunteers may lead to excessive hyper-leukocytosis (>70,000 x10^9/L) without reaching maximum tolerable dose for another AE other than hyper-leukocytosis, which itself may gives rise to the potential risk of splenic enlargement and spontaneous rupture. Accordingly, trials in patients may be required to investigate repeated dosing at higher dose levels".*
GUIDELINE SECTION TITLE: 4. EXPLORATORY CLINICAL TRIALS		
Section 4.1 Para 2 Sentence 1	Effect of treatment on the incidence of neutropenia is an important question to be answered in these clinical studies. Indeed, this draft document identifies "incidence of grade 4 neutropenia…" as the first bullet point in section 4.3, "Endpoints to be Studied on a Regular Basis"	" • Degree • Duration and • Incidence" ***Rapporteur's Comment*** *Accepted* *"incidence added"*
Page 5/10	Modification of neutropenia can not only be modified by the dosage but also the dose regimen.	***Rapporteur's Comment*** *Accepted. "Dose regimen" added* *"The trials should answer questions about how the*

		• *degree and* • *duration* • *incidence* *of the neutropenia can be modified by* • *the dosage or dose regimen"*
Section 4.3	Since differences in PK of HGF could exist between healthy volunteers and patients and before and after chemotherapy, PK data should be collected from the exploratory trials. Immunogenicty data should also be collected from the exploratory trial in patients. 10th and 12th bullet points: please replace "neutrophilic granulocyte count" with "absolute neutrophil count."	The following measures of the differential white blood cell count should be determined in the exploratory trials: ……. • Depth of the nadir of ~~neutrophilic granulocyte~~ absolute neutrophil count • Duration from the beginning of myelosuppressive or myeloablative therapy to the occurrence of nadir • Frequency of a nadir of less than 500 and les than 100 ~~neutrophilic granulocyte~~ absolute neutrophil count per µl • PK data • Immunogenicity data ***Rapporteur's Comment*** *Accepted. Reference to the absolute neutrophil count and collection of PK and immunogenicity data has been added.*
Page 5/10	The last bullet point **duration of the neutropenia* should be upgraded to a second bullet point. Mobilisation of CD34+ cells do not need to be studied on a regular basis. This bullet point may be downgraded in the context of this guideline. Although valuable information, documentation on ability to mobilise CD34 positive stem cells would require a completely different guidance. The determination of 'AUC' of CD34 positive cells, for example, would require longer-term administration of the HGF than what is required for effects on duration and incidence of neutropenia. Importantly due to the	***Rapporteur's Comment*** *Accepted* *Duration of neutropenia has been upgraded to second bullet point.* *Mobilisation of CD34+ has been downgraded and amended as shown below* *"Mobilisation of CD34+ cells (AUC and maximum concentration) where possible"*

	clearance of pegylated HGF's affected by circulating neutrophil counts it may well be that CD34+ stem cell mobilisation is more short lived.	
GUIDELINE SECTION TITLE: 5. CONFIRMATORY TRIALS		
Page 6/10	The benefit/risk issue should be more adequately described in the objectives (see general comments)	***Rapporteur's Comment*** Accepted. Amended as shown below *"The objective of confirmatory trials is the confirmation of the clinical efficacy of the proposed regimen(s) for the new CSF as well as the adverse event profile in the determination of benefit:risk".*
Section 5.1 Para 2 Sentence 1	Efficacy of treatments should also be reflected in a decreasing incidence of febrile neutropenia	"a) significantly reduces incidence, duration, and/or severity of febrile neutropenia… ***Rapporteur's Comment*** *Accepted.* *"incidence" added*

Section 5.1 Para 2 Sentence 1	As written, the phrase "…reduction of frequency of documented infections, days of hospitalization, intravenous antibiotic usage, quality of life or survival" can be read to as that an efficacious treatment will result in reduced quality of life or reduced survival	"…reduction of frequency of documented infections, days of hospitalization or intravenous antibiotic usage, or improvement in quality of life or survival" ***Rapporteur's Comment*** *Accepted. Point clarified as shown below:* *"or improvement in quality of life or survival"*
Section 5.2 First sentence	After option add ':'	 ***Rapporteur's Comment*** *Accepted. and amended*
Section 5.2 Para 3 Sentence 1 Sentence 2	The comment that use of a placebo is acceptable in studies with an incidence of febrile neutropenia less than 20%, and that "there is currently no justification for the use of prophylactic G-CSF if <20% of patients experience febrile neutropenia, as there is no evidence of a clinical benefit" is not appropriate. Currently approved labelling for Neulasta (EU SPC, 28 Oct 2005) includes information from the phase 3 placebo-controlled double blind study of 928 patients by Vogel *et al* (*Journal of Clinical Oncology*, 20 Feb 2005) showing a 94% reduction in the incidence of febrile neutropenia (17% vs. 1%) using a chemotherapy regimen associated with a febrile neutropenia rate of 10-20% (docetaxel 100mg/m^2 every 3 weeks for 4 cycles). Incidence of hospitalisations and intravenous anti-infective use were also correspondingly lower. Additionally, the latest G-CSF clinical guidelines from EORTC, Recommendation 4 states "The risk of complications related to FN should be assessed individually for each patient. When assessing FN risk, the clinician should take into account patient-related risk factors (recommendation 1), the chemotherapy regimen and associated complications (recommendation 2 and 3) and treatment	"If the incidence of febrile neutropenia by regimen is between 10-20% then the use of a placebo arm may or may not be justified. Assessment of individual or study patient characteristics may increase the overall risk of febrile neutropenia to the level where placebo control is no longer ethical, and active comparator may be needed. If the incidence of febrile neutropenia by regimen is less than 10%, then the use of a placebo arm only is acceptable." ***Rapporteur's Comment*** *Accepted in accordance with EORTC and ASCO 2006 guidelines as individual patient characteristics would need to be taken into account and therefore a separate category of neutropenia (10-20%) would need to be considered.* *(For discussion and confirmation by EWP)*

	intent (recommendation 3). If the patient is at >20% overall risk of FN, prophylactic G-CSF is recommended. When using chemotherapy regimens associated with an FN risk of 10-20%, particular attention should be given to the assessment of patient characteristics that may increase the overall risk of FN. Recommendation grade A." Given that patient risk factors are recommended to be included in the assessment of risk of FN, clinically warranted use in regimens associated with a risk of FN below 20% may still be warranted, and categorical denial of G-CSFs to such patients per protocol is not appropriate. Finally, the comment that use of G-CSF in such placebo arms should be dealt with by dose reduction in subsequent cycles is not ethical when treatment intent is curative; maintaining planned doses on-time, with use of G-CSF for any secondary prophylaxis, is in the better interest of the patient.	
Section 5.2 Para 3 Sentence 2 Sentence 3	It is unethical to perform a study that does not allow secondary prophylaxis after an episode of febrile neutropenia or a related event, and discouraging the practice in favour of dose reduction is inappropriate, particularly in any setting where chemotherapy is potentially curative. Additionally, the use of G-CSF prophylactically in subsequent cycles should be specified as "secondary" prophylaxis to avoid confusion.	Should a placebo arm be utilised in a trial of colony stimulating factors, secondary G-CSF prophylaxis for subsequent cycles of chemotherapy should be available by protocol to any patient in the placebo arm that experiences febrile neutropenia or a related event in a prior cycle. ~~Nevertheless, secondary prophylaxis of febrile neutropenia with G-CSF may be used for subsequent cycles of chemotherapy.~~ Dose reduction may also be considered, but primarily for use when chemotherapy is intended to be non-curative (palliative). ***Rapporteur's Comment*** *Accepted in accordance with EORTC and ASCO 2006 guidelines*

Section 5.2 Para 5 Sentence 1	Latest recognized classifications of cytotoxic chemotherapy regimens (EORTC, ASCO) use incidence of febrile neutropenia to categorise myelosupressive intensity, particularly with regard to determining usage of G-CSFs 3	"Cytotoxic regimens can be categorised according to their myelosuppressive intensities; i.e. the incidence of febrile neutropenia." ***Rapporteur's Comment*** *Accepted. " i.e. the incidence of febrile neutropenia" added*
The fifth paragraph	'cytotoxic regimens .. groups' is insufficiently clear. It is to be expected that in a confirmatory trial patients are treated with the same chemotherapy regimen. Therefore 'stratification by intensity of myelosuppressive cytotoxicity' does not seem to be relevant.	***Rapporteur's Comment*** *Not accepted.* *It is preferable but not always possible to include all patients treated with the same chemotherapy regimen and therefore where this has not been possible, patients would need to be stratified by intensity of myelosuppressive cytotoxicity.*

Last paragraph	The last paragraph is insufficiently clear. It is known that haematopoietic growth factors are may also be used – in the context of trials- prior to chemotherapy to prime the cells to the chemotherapeutic agents, but this is quite another issue to be distinguished from use for prevention of FN.	***Rapporteur's Comment*** *Not accepted.* *The purpose is to record the prior use of CSFs to sensitise patients to chemotherapy along with other details of use of standard or high dose chemotherapy*
Section 5.3 Para 5 Sentence 1	The syntax of the current draft implies that "definition of infection and/or fever and definition of leucocyte/neutrophil count" are selection criteria. It is unclear if the meaning is that selection criteria based on infection (history?) and leucocyte/neutrophil counts are suggested for confirmatory studies, or merely that the protocols for such studies need to prespecify such definitions presumably for endpoints (not selection criteria). For purposes of proposed rewording (next column) the latter is assumed.	"The selection criteria should include information regarding prior therapy with HGFs, previous prophylactic treatment (antibacterial/antifungal/other) comorbidity and histological type of tumour (where applicable)." (The remaining text of that sentence should be rephrased to "Definitions of infection and/or fever and leucocyte/neutrophil count should be provided" and placed early in current draft Section 5.5, Primary Endpoints) ***Rapporteur's Comment*** *Accepted. Sentence relocated to section 4.5*
Section 5.6 Para 4 Sentence 2	Inclusion of "occurrence and/or resolution of chemotherapy-induced mucositis" as a secondary endpoint is questionable. It is not an approved indication or recognized treatment or adverse effect of the three G-CSFs currently on the market.	[Remove bullet point of mucositis as a secondary endpoint in confirmatory trials] ***Rapporteur's Comment*** *Not accepted.* *There is an established relationship between degree of neutropenia and mucositis. In addition some trials have shown efficacy with topical administration of G-CSF including mouthwashes which merits further*

		evaluation as a secondary endpoint.
Section 5.7 Para 4 Sentence 1	It appears this sentence, currently under "Immunogenicity", "The safety database is dependent on the experience of the innovator and reference products as well as on the general considerations for recombinant growth factors" should be the last sentence in the prior sub-section of 5.7 (i.e. immediately prior to sub-section of 5.7 on "Immunogenicity")	[Move sentence to end of immediately prior sub-section of Section 5.7, before sub-section of "Immunogenicity".] ***Rapporteur's Comment*** *Accepted. Sentence relocated as requested*
Section 5.7 Para 6 Sentence 3	It is assumed that that immunogenicity safety database that has been specified in the guidance to include between 300-600 patients should be obtained prior to authorisation, as this would provide greater assurance of patient safety.	"While no absolute numbers are specified, the pre-authorisation immunogenicity safety database should include…." ***Rapporteur's Comment*** *Accepted* " pre-authorisation immunogenicity" added to safety database
Section 5.7 Para 6 Sentence 3	Assuming the safety database specified in the guidance will be required pre-authorisation the currently recommended number of patients to be included and the length of follow up are considered adequate and appropriate to assure a sufficient level of patient safety.	[No change proposed to either number or follow-up proposed for pre-authorisation immunogenicity safety database] ***Rapporteur's Comment*** *Noted*

Page 8/10	The Safety Evaluation needs to be extended. The authors do not seem to take into account the development of a number biological agents, e.g. affecting interactions between bone marrow stroma and haematopoietic stem cells, that may have an adverse safety profile. The last sentence on this page include frequency of acute and chronic graft versus host disease. The use of HGF in the context of allogeneic stem cell transplantation deserves separate discussion. It should probably made clear that the initial development of novel HGF's should not done in the much more complex context of allogeneic transplantation.	***Rapporteur's Comment*** *Accepted. See comment below* ***Rapporteur's Comment*** *Accepted. Paragraph amended as follows:* *If applicable and depending on the therapeutic situation (non-infectious), complications of myelosuppressive or myeloablative therapy such as frequency of acute and chronic GVHD, frequency of transplant failure, reactivation of latent viral infection and other opportunistic infections should be analysed and reported. However, the initial development of novel CSFs should not be undertaken in the more complex field of allogeneic transplantation. Additional safety considerations include biological agents which affect interactions between bone marrow stroma and haemopoietic stem cells that may have an adverse safety profile which should be further characterised.*
GUIDELINE SECTION TITLE: 7. COMBINATIONS OF HGFs		
Section 7.1 Para 0	Terms "Additional Effect" and "Additive Effect" in titles of sections 7.1 and 7.2 should be consistent and equivalent.	[Use term "Additive Effect" for both Section 7.1 and 7.2 titles.] ***Rapporteur's Comment***

Title		*Accepted and amended*
GUIDELINE SECTION TITLE: 8. PEGYLATED PRODUCTS		
	The validity of only mentioning pegylated products in this guidance is questioned.	***Rapporteur's Comment*** *Accepted. The relevant section now refers also to "other bioengineered products".* *Additional text has also been included:* *"However, it is appreciated that these guidelines may need to be amended as appropriate when novel haemopoietic growth factors are being studied".*
Para 3 and 4	It is suggested that the PD and PK sections should be combined. Comments on Sections 2 and 3 also apply.	***Rapporteur's Comment*** *Accepted. In line with previous comments to current sections 2 and 3, the PK/PD sections have been combined including changes to assay methodology and inclusion of immunogenicity data.*