European Medicines Agency

London, 5 October 2009
Doc. Ref. EMEA/582443/2008

OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING LOW-MOLECULAR-WEIGHT-HEPARINS

(EMEA/CHMP/BMWP/118264/2007)

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 and EBE	Belgium
2	ESC	France
3	Medicines Board	Netherlands
4	EGA	Belgium
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Table 2:Discussion of comments

GENERAL COMMENTS – OVERVIEW	
Comment and Rationale	**Outcome**
EFPIA/EBE	
General Comment 1: The guidance is limited to non-clinical and clinical aspects and does not address the Quality Standard aspects that biosimilar products must adhere to. This may be misunderstood as "the quality comparability exercise between the biosimilar and the reference LMWHs can be overlooked as long as a non-clinical and clinical comparative program is undertaken". This would be a clear mistake since analytical similarity is the only scientific justification for accepting a reduced non-clinical and clinical program. Biosimilar LMWHs should comply with many of the requirements, particularly with respect to the proof of comparability of Product Quality Attributes as outlined in the guideline on "Similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues" (EMEA/CHMP/49348/05). The general requirements laid down in guideline EMEA/CHMP/49348/05 are also relevant to complex and not fully characterised polysaccharide mixtures such as LMWHs. It should be clarified not only what the guideline addresses but also what it does not address; i.e. the current guideline addresses only the non-clinical and clinical aspects that biosimilar LMWHs must adhere to and does not address quality aspects (The title of the guideline should also be modified accordingly by adding "non-clinical and clinical issues"). The guideline should also explicitly mention that for Quality aspects one should refer to the guideline on "Similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues" (EMEA/CHMP/49348/05).	*BMWP-comment:* *This product-class specific guideline will not further address the quality requirements. For quality aspects the principles are laid down in the general "guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues" (EMEA/CHMP/ 49348/05) , as mentioned in the SCOPE section.*

General Comment 2: We fully support the link that is made in Section 2 of this guideline (Scope) with the guideline on "Similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues" (EMEA/CHMP/42832/05). Indeed the general requirements laid down in guideline EMEA/CHMP/42832/05 are also relevant to complex and not fully characterised polysaccharide mixtures such as LMWHs.	*BMWP-comment:* *Agreement*
General Comment 3: We concur that definite conclusions on the biosimilarity of 2 LMWHs can only be drawn on the basis of data from head-to-head comparative clinical trials in patients. However the guideline proposes that approval could be granted for the biosimilar for all of the indications of the originator product based on clinical comparability for the prevention of VTE in a surgical population. It must be stressed that LMWH are approved not only for venous, but also arterial thrombosis (UA/NSTEMI and STEMI -ACS). The dose of LMWH and even the route of administration in some circumstances (eg. first dose of enoxaparin for STEMI patients) differ from most of those approved for VTE prevention for surgical patients. Furthermore, distinct, but unexpected differences in the efficacy of LMWHs have been observed for the treatment of UA/NSTEMI, with enoxaparin demonstrating superiority to UFH (1), while fraxiparine and dalteparin demonstrate comparable efficacy to UFH (2, 3). The reason for these differences is not fully clarified, but based on the different underlying pathology of venous and arterial thrombosis, and that ACS is a life threatening condition, it would be inappropriate to extrapolate between these indications. More specifically clinical data from studies in venous indications cannot be extrapolated to arterial indications, and vice versa, biosimilarity between 2 LMWHs should be established on the basis of at least two studies, one in a venous indication, the other one in an arterial indication. As a matter of fact, there are major differences in the pathophysiology of venous and arterial thrombosis. Contrary to venous thrombosis which is mainly related to clot formation, platelets adhesion/aggregation and inflammatory response are critical to arterial thrombus formation (4, 5). Heparins possess anticoagulant and non anticoagulant properties. They are ATIII-dependent multitargeted inhibitors of coagulation factors, mainly thrombin and Factor Xa. They also inhibit the coagulation process through ATIII-independent effects such as release of TFPI (Tissue Factor Pathway Inhibitor). Some heparins exhibit anti-inflammatory activity involving interactions with a number of pathways that are independent of ATIII. Those pathways include: interactions with P-selectin, proteins of the complement system, and the contact-kinin system (6, 7, 8, 9).	*BMWP-comment:* *In accordance with the concept of biosimilar medicinal products we are of the opinion that in for a biosimilar LMWH, provided that comparability on the quality, non-clinical and PK/PD panel level has been demonstrated, confirmatory therapeutically equivalence in terms of efficacy and safety could be shown by one clinical trial, which should be performed in the most sensitive clinical setting. Although differences between VTE and ATE could be discussed the BMWP came to the conclusion that the requirements on pharmaceutical quality, non clinical, PK/PD and clinical level now fixed in the guideline are sufficient to make a valid conclusion on biosimilarity between the similar and the reference LMWH.*

Heparins interact indirectly with platelet activation through inhibition of thrombin generation (related to their anti-Factor Xa and anti-thrombin activities). They also impact the platelet aggregation process in an ATIII-independent manner by binding to von Willebrand factor (vWF) preventing interaction between this factor and platelet GPIb receptor. (10, 11, 12).

In conclusion, heparins in general and LMWHs in particular display ATIII-independent effects on key components of the biological processes leading to coronary events.

It has been established that the extent of these effects vary not only between UFH and LMWH but also between LMWH (11, 12). These data explain at least partially the differences in clinical outcome observed in several randomized, double-blind, comparative studies in patients with unstable angina or myocardial infarction without ST segment elevation (1, 2, 3, 13) as well as in patients with ST segment elevation myocardial infarction (14).

The effects discussed above cannot be assessed and compared in the setting of a venous indication. Consequently a biosimilar LMWH and the originator product should also be compared in ACS patients.

1. Cohen et al. ; N. Eng. J. Med. ; Vol. 337 (7); August 1997; pages 447-452
2. Heart J.; 1999 (20); pages 1553-1562
3. Klein W et al.; Circulation; 1997 (96); pages 61-68
4. Buffon et al.; N. Eng. J.Med ; Vol 347 (1); July 2002; pages 5-12
5. Libby & Theroux; Circulation; Vol. 111; June 2005; pages 3481-3488
6. Hostettler et al.; FASAB Journal; Vol. 21; November 2007; pages 3562-3572
7. Bergamaschini et al.; J. Neurosci.; Vol. 24 (17); April 2004; pages 4181-4186
8. Ludwig et al.; Mini-Reviews in Medicinal Chemistry; Vol. 6 (9); 2006; pages 1009-1023
9. Libersan et al.; Cardiovascular Research; Vol. 37; 1998; pages 656-666
10. Sobel et al.; Circulation; Vol. 93 ; 1996 ; pages 992-999
11. Montalescot et al.; Circulation ; Vol. 98 ; 1998 ; pages 294-299
12. Montalescot et al. ; Am. J. Cardiol. ; Vol. 91 ; April 2003; pages 925-930
13. Michalis et al.; Am. Heart J.; 146 (2); August 2003; pages 304-310
14. Antman et al., N. Eng. J. Med. ; Vol. 354 (14); April 2006; pages 1477-1488

General Comment 4: Add more specifics around **Non-clinical and Clinical Issues** for *LMWH* (based on EMEA/CHMP/BWP/42832/05), such as **Biological activity(ies)** (e.g. anti-Xa, anti-IIa, TFPI, thrombin generation, tPA, PAI, vWF, PF4-interaction), Purity and Impurities (e.g. OSCS, ruminant and non-ruminant DNA, etc.), PK/PD (e.g. Half-life and CL_{Total} : (based on anti-Xa, anti-IIa, as well as global antithrombotic effects); Renal and non-renal Clearance, Accumulation with long-term use in renal impairment, etc.).	*BMWP-comment:* *The BMWP disagrees with this proposal and is of the opinion that the requirements on non-clinical, clinical issues (and especially with regard to the biological activities) now included in the guideline are adequate and sufficient*
General Comment 5: Extrapolating the results of one study using a **low dose** will not provide evidence (efficacy) for use in **high-dose indications** (e.g. Treatment of DVT/PE or Cancer-associated thrombosis or ACS); The following data provides support for this view: 1) "The differences in the relative pharmacokinetics and pharmacodynamics of these [LMWH] drugs are becoming more obvious in such indications where relatively higher doses and extended treatment modalities are used." (Fareed & Bick, Clin Appl Thrombosis/Hemostasis 2004) 2) " Differences in aIIa and aXa peak activities are more striking when high doses of LMWHs are used. The activated partial thromboplastin time (aPTT) can be significantly prolonged, an effect that is related to aIIa and aXa activity". (Samama et al. Semin Thromb Hemost 2000; Volume 26: 031-038)	*BMWP-comment:* *As dose response curves are non- linear the PK/PD of the surrogate parameters should be compared in two randomised single dose two way crossover studies using one dose in the prevention (lower) range with subcutaneous administration and one dose in the therapy (upper) range of efficacy with intravenous administration. Therefore the comparability aspects addressed in this comment are included adequately in the guideline.*
The introduction mentions bleedings as the most common and HIT II as the most serious adverse reaction. This neglects the fact that bleedings can be fatal or can cause permanent disability (e.g. due to cerebral bleeding). As this was not considered only one study investigating a prophylactic dose in a surgical setting was assumed to be sufficient to provide a premarketing safety data base. Fatal events or cerebral bleedings predominantly occur in indications with high doses of LMWH such as NSTEMI and treatment of VTE. The bleedings may be provoked by pharmacokinetic differences in elderly and/or patients with moderate severe renal insufficiency. Therefore, studies have to be performed in these indications including a sufficient number of patients with different degrees of renal impairment exposed for several days to show that a product is biosimilar with regards to bleeding. Special consideration should also be given to indications with long-term exposure; haemodialysis/haemofiltration and the extended treatment of VTE in cancer patients for 6 months.	*BMWP-comment: We disagree with the proposals made here. One should remember that this guideline refers to a biosimilar medicinal product. In this product class sufficient experience with the reference LMWH is available on all the aspects addressed. This could be extrapolated to the biosimilar product, provided similarity has been sufficiently demonstrated..*

EGA	
In general, the clinical data requirements appear to be excessive for this class of medicines and not in keeping with requirements in other regulatory jurisdictions. These molecules are well characterised with respect to their structure, physico-chemical properties, mechanism of action and pharmacological effects. We suggest that the guideline should reflect the ability to characterise these products at both the physico-chemical and pharmacological levels. The proposed guideline should allow an approach using PK/PD studies rather than requiring large scale phase III safety and efficacy trials. Certainly the guideline should permit a waiver for large-scale safety and efficacy phase trials if the animal source and the method of synthesis for the product are the same as those for the reference product, and provided that an extensive in vitro characterisation comparability exercise supports the "sameness" of the two products. Since these molecules have a well-established clinical profile, there is no need to carry out clinical studies to demonstrate basic safety and efficacy. Furthermore, in the introduction (paragraph 12) it states that "…it is uncertain whether the PD markers are representative of clinical outcome." There is considerable evidence to support the usual view that PK/PD markers are highly consistent and predictive indicators of clinical outcome for LMWH. We therefore recommend that clinical efficacy studies should not be a specific requirement for approval and that human PK/PD studies should be sufficient.	*BMWP-comment:* *We disagree with the proposal that clinical efficacy studies should not be a specific requirement for approval and that human PK/PD studies should be sufficient. As other biosimilar medicinal products LMWHs have to prove comparability with regard to efficacy and safety in a clinical trial.*
ESC	
The European Society of Cardiology, and in particular its Working Group on Thrombosis, welcomed the opportunity to comment on this guideline. It has been well received and assessed as a well written and well balanced guideline for the demonstration equivalence of two different LMW heparin products. However, the major hurdle for the comparison of different LMWH products is the lack of an agreed international LMWH standard to which each individual LMWH product can be adjusted to. Furthermore, today, each LMWH producer declares individual units that are not standardized. It therefore should be stated, that this guideline is only valid until such an international agreed LMWH standard exists.	*BMWP-comment:* *Although an international agreed LMWH standard will be an important improvement we do not agree that such a development will directly affect the validity of this guideline.*

SPECIFIC COMMENTS ON TEXT		
TITLE OF THE GUIDELINE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
Title (page 1)	Refer to General Comment 1 above.	

[1] Where applicable

(EFPIA)	***Proposed change*** GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING LOW-MOLECULAR-WEIGHT-HEPARINS **(Non-Clinical and Clinical Issues)**	

SPECIFIC COMMENTS ON TEXT		
EXECUTIVE SUMMARY		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Page 3 **(EFPIA)**	Refer to General Comment 1 above ***Proposed change*** This guideline lays down the non-clinical and clinical requirements for low molecular weight heparins (LMWHs) containing medicinal products claiming to be similar to another one already marketed. **It does not address the quality requirements.** The non-clinical section addresses the pharmaco-toxicological requirements and the clinical section the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies as well as pharmacovigilance aspects.	*BMWP-comment:* *Proposal not included, however for quality issues refer to the wording in the SCOPE section, please.*

SPECIFIC COMMENTS ON TEXT		
1 INTRODUCTION		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Introduction 1st § (page 3) **(EFPIA)**	Heparin consists in various disaccharide units which are located according to the biosynthetic modifications of the chain backbone; consequently the word "repeating" should be deleted. ***Proposed change*** Heparin is a highly sulphated and heterogeneous member of the glycosaminoglycan family of carbohydrates consisting of various ~~**repeating**~~ disaccharide units.	*BMWP-comment:* *Proposal included*

Introduction 2nd § (page 3) **(EFPIA)**	The reference to domestic animals, principally porcine product – some of these products contain non-porcine heparin ***Proposed change*** Suggest…porcine and other animal product…	*BMWP-comment:* *Proposal included as "mainly from porcine mucosa".*
Introduction 3rd § (page 3) **(EFPIA)**	Several isoforms of the pentasaccharide sequence have been identified; consequently the word "specific" should be deleted. ***Proposed change*** For the binding of heparin to AT a ~~**specific**~~ pentasaccharide sequence, which contains a 3-O-sulphated glucosamine residue, is important.	*BMWP-comment:* *Proposal included*
Introduction 3rd § (page 3) **(EFPIA)**	In addition to their effects on factors Xa & IIa, it should be mentioned that heparins achieve their anticoagulant effects via other AT-mediated (e.g. TAFI) and non AT-mediated (TFPI, hep cofactor II) properties. (1, 2, 3) 1. Jeske et al.; Biochemical an Pharmacological differentiation of generic LMWHs; XXIst ISTH Congress; Geneva; July 2007 2. Mousa & Kaiser; Drugs of the Future; Vol. 29 (7); 2004; pages 751-766 3. Tobu et al.; Clin. Appl. Thrombosis/Hemostasis; Vol. 11 (1); 2005; pages 37-47 ***Proposed change*** ….. after the serine-protease attacks a specific Arg-Ser peptide bond in the reactive site of antithrombin. <u>Furthermore heparins may have other anticoagulant properties either mediated by AT-dependent inhibition of factor Xa/thrombin, e.g. reduced activation of thrombin activatable fibrinolytic inhibitor (TAFI), or not mediated by AT such as tissue factor pathway inhibitor (TFPI) release, acceleration of heparin cofactor II inhibition.</u>	*BMWP-comment:* *Proposal not included as information given already seems to be detailed and specific enough for the purpose of this guideline*
Introduction 3rd § (page 3) **(EFPIA)**	Refer to General Comment 3 above ***Proposed change*** In addition, heparin has numerous other plasmatic and cellular interactions, but overall, in comparison with the anticoagulatory effect, the clinical relevance of these interactions is ~~**uncertain**~~ <u>not fully understood</u> and insufficiently investigated.	*BMWP-comment:* *Original wording retained.*
Introduction 4th §	Heparin is also administered intraarterialy in indications such as Coronary Artery Bypass Graft or haemodialysis.	*BMWP-comment:* *Proposal included*

(page 3) **(EFPIA)**	***Proposed change*** Heparin is administered parenterally, as it is degraded when taken orally. It can be injected intravenously, intraarterialy or subcutaneously, whereas intramuscular injections should be avoided because of the risk of inducing hematomas.	
Introduction 7th § (page 3) **(EFPIA)**	The 1st sentence may be misunderstood as "the existing state of the art methods allow a full characterisation of LMWH products". In the 2nd sentence "subfractions" should be replaced by "polysaccharides" as in a given subfraction there is a large diversity of polysaccharide with different chemical structures and pharmacological behaviours (whatever the method used to isolate the subfraction). ***Proposed change*** While several state of the art methods for physico-chemical characterisation of LMWH products are available, they do not enable a full characterisation of the polysaccharide chains in the mixture. ~~**However, it**~~ It is presently not known to which extent the multiple different ~~**subfractions**~~ polysaccharides contribute to the clinical efficacy of LMWH.	*BMWP-comment:* *Proposal not included, original wording retained.*
Introduction 8th § (page 3) **(EFPIA)**	The 1st sentence should be modified to take into consideration LMWH with relatively high molecular weight such as tinzaparin. In the 2nd sentence, "a more selective" should be replaced by "an increased". Indeed LMWH heparins achieve their effects via a wide range of pharmacological properties. ***Proposed change*** A specific LMWH differs from unfractionated heparin and from other LMWHs in its pharmacokinetic and pharmacodynamic properties. As a result of the depolymerisation process they normally ~~**contain mainly**~~ are enriched in molecules with less than 18 monosaccharide units. This reduction of molecule size is associated with a loss of thrombin inhibition activity in comparison to standard heparin and ~~**a more selective**~~ an increased inhibition of Xa.	*BMWP-comment:* *Proposal included*
Introduction 9th § (page 4) **(EFPIA)**	This paragraph should indicate that pharmacodynamic tests are surrogate tests as they do not correspond to the whole product mixture but only to parts of it (e.g. Anti-Factor IIa activity does not account for the polysaccharides with no AT affinity or with less than 18 monosaccharides. Similarly, polysaccharides bearing the anti-FXa and anti-FIIa activities, are only representative of about 20% of the overall polysaccharidic mixture in a given LMWH). ***Proposed change*** Due to difficulties in the physical detection of the various polysaccharides contained in LMWH, conventional pharmacokinetic studies cannot be performed. Instead, the absorption and elimination of LMWHs are studied by using surrogate pharmacodynamic	*BMWP-comment:* *Original wording retained.*

	tests, including anti-FXa and anti-FIIa activity.	
Introduction 10th § (page 4) **(EFPIA)**	LMWHs do not only differ in terms of pharmacodynamic properties but also in terms of the evolution upon time of the extent of these potencies, i.e. they differ in terms of their pharmacokinetics. One LMWH, enoxaparin, is approved in the treatment of acute STEMI. ***Proposed change*** There are several authorised LMWHs that differ in their source material, manufacturing process, pharmacokinetic/pharmacodynamic properties and therapeutic indications, which include treatment and prophylaxis of deep venous thrombosis and prevention of complications of acute coronary syndromes (unstable angina ~~**and**~~ , non-STEMI and STEMI) ~~**non-Q wave cardiac infarction and**~~.	*BMWP-comment:* *Proposal included*
Introduction 11th § (page 4) **(EFPIA)**	In addition to HIT, major bleedings should also be considered as being part of the most serious adverse reactions. ***Proposed change*** The most common adverse reactions of heparins are bleedings, from minor to life-threatening ones. Another serious adverse reaction, whilst ~~**the most serious one is the**~~ rarely observed is Heparin-induced thrombocytopenia type II (HIT ÌI).	*BMWP-comment:* *Original wording retained.*
Introduction 12th § (page 4) **(EFPIA)**	Refer to General Comment 3 above ***Proposed change*** In conclusion, the heterogeneity of LMWH is very high, the mode of action is not completely understood and it is uncertain whether the PD markers are representative for the clinical outcome. Thus, the major burden of demonstrating two LMWHs being similar biological medicinal products is on ~~**a**~~ the clinical ~~**trial**~~ program.	*BMWP-comment:* *Proposal not included*
Chapter 1 Para 3 Line 3 Line 9 **(ESC)**	Further useful details ***Proposed change*** …only about one third of the heparin molecules possesses the pentasaccharide sequence… …treatment and profilaxis of deep vein thrombosis and pulmonary embolism…	*BMWP-Comment:* *Although these details might be appreciated as useful the BMWP has dispensed from their inclusion for the sake of shortness of the text.*

Page 4, para3, line 4/5 **(ESC)**	PF4-heparin-complex antibodies are a prerequisite for HIT but such PF4-heparin antibodies can be found in many more patients (up to 40%) than develop HIT ***Proposed change*** The sentence should read: Binding of those antibody-PF4-heparin complexes may activate platelets	*BMWP-Comment:* *The proposal was included.*
SPECIFIC COMMENTS ON TEXT		
2 SCOPE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Page 4 **(EFPIA)**	Refer to General Comment 1 above ***Proposed change*** The guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CPMP/42832/05/) lays down the general requirements for demonstration of the similar nature of two biological products in terms of safety and efficacy. This product specific guidance complements the above guideline and presents the current view of the CHMP on the application of the guideline for demonstration of comparability of two LMWH-containing medicinal products. It does not address the quality requirements. For quality aspects one should refer to the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance :Quality issues" (EMEA/CHMP/49348/05).	*BMWP-comment:* *Proposal included*
Page 4 **(EFPIA)**	"This product specific guidance complements the above guideline and presents the current view of the CHMP on the application of the guideline for demonstration of comparability of two LMWH containing medicinal products": the term "comparability" relates to the comparison of a product before and after a manufacturing change. Products resulting from different manufacturing processes can never be shown to be "comparable", but just to be "similar" (by a comparability exercise). ***Proposed change*** Replace "comparability" with "biosimilarity".	*BMWP-comment:* *Proposal included*

SPECIFIC COMMENTS ON TEXT		
3 LEGAL BASIS		
Line no. + para no.	**Comment and Rationale**	**Outcome**

SPECIFIC COMMENTS ON TEXT		
4 NON-CLINICAL STUDIES **PHARMACODYNAMIC STUDIES**		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.1 Non-clinical studies (page 4) **(EFPIA)**	Non-clinical testing and Bioassays are critical in this guideline, especially when considering non-anticoagulant mechanisms (e.g. angiogenesis, anti-inflammatory effects, anti-tumour/anti-metastatic effects, apoptosis) of certain LMWHs**.** "In addition, heparin has numerous other plasmatic and cellular interactions, but overall, in comparison with the anticoagulatory effect, the clinical relevance of these interactions is uncertain and insufficiently investigated." (EMEA/CHMP/BMWP/118264/2007) "The non-anticoagulant biological effects of these drugs are poorly understood at this time."(Fareed & Bick, 2004) "Heparin has been used for more than 50 years; however, its chemical and biologic attributes are not fully understood even at this time. Knowledge of the structure of heparin has been useful, but these properties do not fully characterize heparin in terms of pharmacological effects." "Unlike generic drugs that are simpler and mostly used for specific indications, the LMWHs have broad indications… and are approved for different indications. While these [LMWHs] may have similar composition, molecular weight, and other chemical attributes, these mixtures may have biophysical differences despite similar composition." (Fareed et al, Clin Appl Thrombosis/Hemostasis 2005). ***Proposed change***	*BMWP-comment:* *Proposal partially included.* *In accordance with the proposal of EFPIA/EBE, the revised GL text now defines the minimum requirements for non-clinical pharmacodynamic evaluation. Based on state of the art knowledge about clinically relevant pharmacodynamic effects of LMWHs, additional evaluations may be performed by / requested from the Applicant. However, taking into account that data from an extensive quality comparability exercise is available, it does not appear feasible / necessary to ask for an evaluation of all currently documented pharmacodynamic effects of LMWH, which may or may not be related to their clinical efficacy, in the context of the non-clinical comparability exercise.*

	Provide more detail and specifics on Non-clinical testing and Biological activity tests that may be *required*, or *optional*, for applicants to demonstrate comparability to the reference LWMH.	
Pharmacodynamic studies (Section Title) page 4 **(EFPIA)**	See above comment on [Introduction 10th §] ***Proposed change*** **<u>Pharmacokinetic/</u>Pharmacodynamic studies**	*BMWP-comment:* *Original wording retained.* *Due to difficulties in physical detection of LMWHs, conventional pharmacokinetic/ toxicokinetic studies are not meaningful and are not part of the non-clinical comparability exercise for biosimilar LMWHs.*
Pharmacodynamic studies "In vitro studies" section (page 4). 1st sentence **(EFPIA)**	"In order to compare any alterations in activity between…" ***Proposed change*** the word "any" be removed from this sentence	*BMWP-comment:* *GL text was modified as proposed.*
Pharmacodynamic studies "In vitro studies" section (page 4) **(EFPIA)**	Add clarity on specific *required* and *optional* testing to be performed. The tests indicated/currently available may not be able to test for all alterations in activity between the similar and reference product. A more comprehensive list of potential assays should be provided. In order to detect possible differences at an early stage of development in addition to bioassays submitted as part of the quality dossier and conducted in purified systems, it is also important conduct tests in human plasma and/or whole blood as well as more functional tests, e.g. thrombin generation test. (1, 2) 1. Hemker et al.; Pathophysiol. Haemost. Thromb.; 2003; Vol. 33; pages 4-15 2. Hemker & Béguin; Thromb. Haemost.; 2000; Vol. 84; pages 747-751 ***Proposed change*** *In vitro* studies: In order to compare any alterations in activity between the similar biological medicinal product and the reference LMWH, data from a number of comparative bioassays (e.g. for anti-Xa and anti-IIa activity), many of which may already be available from	*BMWP-comment:* *See comment on point "4.1 Non-clinical studies".*

	bioassays submitted as part of the quality dossier, should be provided. Standardised assays (e.g. in accordance with the European Pharmacopoeia) should be used to measure activity. Bioassays (e.g. for anti-Xa and anti-IIa activity, heparinase inactivation, protamine neutralisation) should also be performed in human plasma. Furthermore more functional assays such as the thrombin generation test should be conducted in order to confirm that anti factor Xa/IIa activity corresponds to an anticoagulant effect in plasma, platelet-rich plasma or whole blood.	

Pharmacodynamic studies "In vivo studies" section (page 5) **(EFPIA)**	As above; add clarity on specific *required* and *optional* testing to be performed. The tests indicated/currently available may not be able to test for all alterations in activity between the similar and reference product. A more comprehensive list of potential assays should be provided. LMWHs display a large spectrum of interactions with plasmatic and cellular components resulting in anti-coagulant as well as non-anticoagulant pharmacological properties. Although the major burden for demonstrating biosimilarity is on the clinical program, the 2 products should be compared in pharmacodynamic models and in suitable animal models (including venous and also arterial thrombosis models if the reference product is used in arterial indications). These comparisons would allow to detect possible differences at an early stage of development and to make sound decisions as to whether or not development should proceed to the clinical phase. ***Proposed change*** *In vivo* studies: The *in vivo* <u>pharmacokinetic/</u>pharmacodynamic activity of the similar biological medicinal product and the reference LMWH should be quantitatively compared in • an appropriate *in vivo* pharmacodynamic model (e.g. by evaluation of pharmacodynamic markers such as anti-Xa and anti-IIa activity and TFPI (in extenso). If feasible, these evaluations can be performed as part of the described repeat dose toxicity study. and~~/or~~ • a suitable animal venous <u>thrombosis model</u> ~~or~~ <u>and a suitable</u> arterial thrombosis model <u>if the reference product is used in arterial indications. In addition evaluation in appropriate bleeding models compared to the originator product must also be investigated</u>.	*BMWP-comment:* *Proposal not included.* *Concerning the statement that the tests indicated/currently available may not be able to test for all alterations in activity between the "biosimilar" and the reference product, see comment on point "4.1 Non-clinical studies".* *Taking into account that data from an extensive quality comparability exercise will be available, demonstration of similar activity of the "biosimilar" and the reference LMWH in either a pharmacodynamic in vivo model <u>or</u> an in vivo thrombosis model appears sufficient for the non-clinical comparability exercise. Furthermore, based on the same arguments, even if the "biosimilar" product is intended to be used in both venous and arterial indications, non clinical evaluation in either a venous or an arterial animal thrombosis model appears sufficient. Finally, an inclusion of specific "bleeding models" is not expected to provide relevant additional information, taking into account that the toxicological properties of "biosimilar" and reference LMWH are compared in a repeated dose toxicity study (see below).*
Section 4.1: Pharmacodynamic studies **(EGA)**	The requirement for an *in vivo* PD study in animals is redundant if a human PK\PD study is mandated. The human study is more sensitive in detecting differences in performance between products and relevance to the use of the products than the animal study. ***Proposed change***	*BMWP comment:* *Proposal not accepted.* *The comparability exercise follows a stepwise approach. For the sake of human welfare, similar in vivo pharmacodynamic activity of "biosimilar" and*

	Delete the requirement of the in vivo PD study in animals.	*reference LMWH should be established at the non-clinical level before starting pharmacodynamic evaluations in humans.*
(MB)	For the sake of animal welfare, PD and toxicology studies should be combined as much as possible for biosimilarity applications	*BMWP-comment:* *The GL text has been modified accordingly.*
SPECIFIC COMMENTS ON TEXT		
4 NON-CLINICAL STUDIES **TOXICOLOGICAL STUDIES**		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Toxicological studies 1st § (page 5) **(EFPIA)**	Study duration: It is suggested that the duration of the study be sufficient as to justify the indication, however this may be at odds with a later statement in the guidance concerning the applicability of the similar product for all of the reference products indications. Dalteparin has the indication for the prevention of recurrence of VTE in patients with cancer; this use is up to 6 months. Route of administration: The route of administration for the repeat dose toxicity study is not specified and may be understood as the SC route. However it has been observed that the toxicological effects related to some impurities, especially those with a high molecular weight, may remain undetected when the product is administered via the SC route whereas they become apparent via the IV route. Consequently toxicity should also be investigated via the IV route, especially if the reference product is used via the IV route (e.g. STEMI) or the intraarterial route. ***Proposed change*** Data from at least one repeat dose toxicity study via the subcutaneous route in a relevant species (e.g. the rat) should be provided. ~~Study duration should be chosen in accordance with the intended duration of clinical application, however, should be at least 4 weeks.~~ Study duration should be in accordance with the longest duration of use of the reference products intended duration of clinical application. In case of short duration of all intended clinical applications study duration should not be shorter than 4 weeks. Toxicity should also be investigated via the intravenous route, especially when the reference product is used via this route or the intraarterial route of administration. The	*BMWP-comment:* *Proposal not included.* *In accordance with the "Note for guidance on repeated dose toxicity", in general the medicinal product should be administered by the same route as that intended for humans. In case different routes of application are intended for humans, the type of application expected to result in the highest systemic exposure should be chosen for the repeated dose toxicity study. In addition, for all intended forms of parenteral application the local effects at the site of administration should be evaluated (see "Note for guidance on non-clinical local tolerance testing of medicinal products", CPMP/SWP/2145/00).*

	studies should be performed in accordance with the requirements of the "Note for guidance on repeated dose toxicity" (CPMP/SWP/1042/99).	
Toxicological studies 1st § (page 5) **(EFPIA)**	The guideline states that 'Special emphasis should be laid on the determination of effects on blood coagulation/hemostasis and on potential development of osteoporosis'. As only very marked effects on the potential to develop osteoporosis could be detected in a 4 week study, clarification of the models to be used would be beneficial. There are several other class-specific effects other than those mentioned in the current draft. ***Proposed change*** Special emphasis should be laid on the determination of effects on blood coagulation/hemostasis and on ~~**potential development of**~~ ~~**osteoporosis**~~ all the other important effects known to occur for this class of product.	*BMWP-comment:* *Proposal included in modified form (see revised GL text).*
Toxicological studies 2nd § (page 5) **(EFPIA)**	It is likely that the repeat dose toxicity study will be conducted in rat. This species is not very sensitive with respect to local tolerance. ***Proposed change*** Data on local tolerance in at least one sensitive species should be provided in accordance with the "Note for guidance on non-clinical local tolerance testing of medicinal products" (CPMP/SWP/2145/00). If feasible, local tolerance testing can be performed as part of the described repeat dose toxicity study provided that the study is conducted in a sensitive species.	*BMWP-comment:* *Original wording retained.* *While it is agreed that the non-clinical local tolerance testing should be performed in a species which reflects the human situation, the "Note for guidance on non-clinical local tolerance testing of medicinal products" (CPMP/SWP/2145/00) does not explicitly request to perform local tolerance studies in a species which is sensitive (i.e. showing a pharmacological and/or toxicological response) to locally applied LMWHs.*
Section 4.1: Toxicological studies **(EGA)**	The requirement of local tolerance testing should not be needed if the formulation is sufficiently similar (Q1 and Q2 compliant) to that of the reference product. ***Proposed change*** Delete the requirement for local tolerance testing if the formulation is equivalent (Q1 and Q2) with respect to the reference product.	*BMWP comment:* *Proposal not accepted.* *The comparability exercise follows a stepwise approach. Local tolerability of a "biosimilar" LMWH cannot be predicted on basis of quality data alone. For the sake of human welfare, similar local tolerability of "biosimilar" and reference LMWH should be established at the non-clinical level before starting application to humans.*
(MB)	The rationale behind the comparison of biosimilar and marketed LMWH considering the	*BMWP-comment:*

	potential to develop osteoporosis is not clear. Although chronic treatment with high doses heparin resulted in osteoporosis, and a weak osteopenic effect was observed with Fragmin (as described in the Dutch SPC text) and with heparin, these effects were only described for 6 month dog studies. Whether a discriminating effect will be observed in a (4 week) rodent study is not certain, and it is not feasible to request 6 month data for this purpose. ***Proposed change*** To our opinion, this osteoporosis is more of an issue if a new LMWH is being developed, then it would be feasible to compare with other LMWH and/or heparin. Therefore it is too much to ask to put 'special emphasis' on the potential development of osteoporosis for a biosimilar LMWH application.	*Proposal partially accepted..* *It is agreed that it is uncertain whether an osteopenic effect/osteoporosis can be detected in a 4 week rodent repeated dose toxicity study. However, as stated in the current GL text, study duration should be chosen in accordance with the intended duration of clinical application. This means that in case of an intended long-term clinical application of the "biosimilar" LMWH, a subchronic/chronic repeated dose toxicity study should be a component of the non-clinical comparability exercise. In such a study, known potential long-term adverse effects of LMWHs, like e.g. development of osteoporosis, should be monitored.* *I thought this has been deleted!*

SPECIFIC COMMENTS ON TEXT		
5 CLINICAL STUDIES PHARMACOKINETIC/PHARMACODYNAMIC STUDIES		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Pharmacokinetic/Pharmacodynamic studies 1st § (page 5) **(EFPIA)**	It should be more explicitly mentioned that PD tests should not be limited to anti-FXa and anti-FIIa activities. In addition, due to the high heterogeneity of the polysaccharide chains assessment of the PD parameters will not allow to discriminate between specific molecular species but rather between subsets of the polysaccharidic mixture. ***Proposed change*** Due to the heterogeneity of LMWHs conventional pharmacokinetic studies cannot be performed. Instead, the absorption and elimination characteristics of LMWHs should be compared by using their pharmacodynamic ~~**tests**~~ activities (including anti-FXa and anti-FIIa), as surrogate markers for their circulating concentrations. ~~**PK/PD assessment such**~~	*BMWP-comment:* *Proposal included*

	~~**as anti-FXa and anti-FIIa activity and**~~ In addition other pharmacodynamic tests such as Tissue Factor Pathway Inhibitor (TFPI) activity~~**. In addition,**~~ as well as the ratio of anti-FXa and anti-FIIa activity should be compared. Assessment of these PD parameters will provide a fingerprint of the different ~~**molecular species**~~ subsets of the polysaccharidic mixture.	
Pharmacokinetic/Pharmacodynamic studies 2nd§ (page 5) **(EFPIA)**	Due to parameters such as selectivity in absorption or presystemic biotransformation, for 2 distinct LMWHs the pharmacokinetic behaviour of some surrogate markers, e.g. anti-FIIa activity, may be similar via a given route, e.g. sc, but differ via a different route, e.g. iv. (Sanderink et al.; Clinical Pharmacology & Therapeutics; Vol. 72 (3); 2002; pages 308-318) Consequently a comparison between the 2 products should also be performed via the IV route, especially if the reference product is used via the IV route (e.g. STEMI) or the intra-arterial route. These pharmacokinetic/pharmacodynamic properties of the similar biological medicinal product and the reference product should be compared in a randomized, single dose two way crossover study in healthy volunteers using subcutaneous administration. In case the originator product can be administered to patients via the IV or intra-arterial route, a comparative study should be performed via the IV route.	*BMWP-comment:* *Proposal included*
Pharmacokinetic/Pharmacodynamic studies 2nd§ (page 5) **(EFPIA)**	Pharmacokinetic/pharmacodynamic studies should be conducted as multi-dose studies to assess bioaccumulation, especially in elderly patients and patients with renal impairment. ***Proposed change*** In addition, surrogates for PK should be assessed in clinical trials performed in the specific indication. Specific data on bioaccumulation, especially in elderly patients and in patients with renal insufficiency, should be supplied.	*BMWP-comment:* *Proposal not included.* *A biosimilar LMWH needs to show similarity regarding quality, safety and efficacy. Comparative PD studies in healthy volunteers are recommended in the guideline to investigate potential differences in PD properties between the biosimilar and the reference product. However, based on demonstrated similarity, not all studies performed with the reference product need to be repeated with the biosimilar. Studies in special populations are not considered necessary.*
Chapter 4.2 Pharmacodynamic	The relationships between structure and the different complex biological effects of LMWH is incomplete, it cannot be claimed that different measurable pharmacodynamic effects are strictly related to clinical efficacy and safety (e.g. anticoagulative effects such	*BMWP-Comment:* *The guideline includes some well measurable pharmacodynamic effects with relevance for arterial*

(ESC)	as fXa, thrombin inhibition). the different anticoagulant activities of different approved LMWH preparations cannot be used to fully predict the clinical effects of a certain preparation. The recommended dose regimens for the different approved preparations have been justified in clinical trials covering each approved indication. ***Proposed change*** An equivalence study comparing the pharmacodynamic profiles of the anticoagulant effects of the new and a relevant reference product (EU approved) along the lines proposed should be provided (by comparing e.g. anti-Xa and anti-IIa activities, global coagulation tests) Such a study should be performed at more than one relevant dose level. Clinical characterisation of the efficacy and safety for the product claimed to be biosimilar would is also required.	*and venous thromboembolism. Assessment of these PD parameters will provide a fingerprint of the different molecular species covering some relevant PD aspects. A comparison should be made for subcutaneous and intravenous administration with different doses. Insofar the proposal is included in the guideline.* *However, since none of the PD parameters is an accepted surrogate parameter for efficacy, similar efficacy (and safety) needs to be demonstrated in a comparative clinical trial using a sensitive test model.*
Chapter 4.2 Pharmacokynetic **(ESC)**	Different LMWH products may be cleared from the blood with different elimination rates, hence some may accumulate in renally impaired patients while others do not. ***Proposed change*** Pharmacokinetics should also be tested in rennaly impaired individuals (clearance 30 – 60 ml/min) and elderly patients (age > 75 years).	*BMWP-Comment:* *See comment above. Studies in special populations are not considered necessary for a biosimilar.*
Chapter 4.2 Pharmacokynetic Line 8 **(ESC)**	LMWH doses vary in DVT prevention and DVT treatment or prevention of arterial thromboemboli. It is of importance that the dose response curves are non linear ***Proposed change*** ….should be compared in two randomised single dose two way crossover studies using one dose in the prevention (lower) range and one dose in the therapy (upper) range of efficacy…….	*BMWP-Comment:* *The proposal was included, however the wording differs.*

SPECIFIC COMMENTS ON TEXT		
5 CLINICAL STUDIES **CLINICAL EFFICACY**		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Clinical	Refer to General Comment 3 above	*BMWP-comment:*

efficacy 1st § (page 5) **(EFPIA)**	Refer to General Comment 5 above ***Proposed change*** Since a clear correlation between surrogate PK/PD parameters (antifactor Xa or IIa) and clinical outcome has not been established, a similar biological medicinal product containing LMWH should show equivalent efficacy and safety to a reference product approved in the EU. This therapeutic equivalence should be demonstrated in ~~**at least one**~~ adequately powered, randomised, double-blind, parallel group clinical trials. In theory, this ~~**could**~~ should be done either in the setting of prevention ~~**of venous**~~ or treatment of venous thromboembolism and in the setting of arterial thromboembolism, depending on the type of indications of the reference product~~**, or in the setting of treatment of venous thromboembolism. However, the**~~ The most sensitive models to detect potential differences in efficacy between the new LMWH and the reference product should be selected. With respect to venous thromboembolism, **s**urgical patients have the highest prevalence of venous thromboembolism (VTE). Furthermore, the vast majority	*Original wording retained. (see comments above on two clinical trials item)…….*
Clinical efficacy 3rd§ (page 6) **(EFPIA)**	It should be ensured that a significant proportion of fragile patients is included in the clinical program. ***Proposed change*** Therefore, it is recommended to demonstrate efficacy in the prevention of VTE in patients undergoing surgery with high VTE risk. Preferably, the trial should be conducted in major orthopaedic surgery such as hip surgery. In this clinical setting, patients with hip fracture should be well represented in the study as they have both high thrombotic risk and high perioperative bleeding risk. The posology and administration should follow European recommendations for prophylaxis with the reference product in patients requiring prolonged VTE prophylaxis. It should also be ensured that a sufficient proportion of fragile patients is included (e.g. elderly, renal impaired, etc.).	*BMWP-comment:* *Original wording retained as sufficient; because patients with hip fracture are usually elderly, more fragile patients.*
Clinical efficacy (page 6) **(EFPIA)**	Refer to General Comment 3 above. Add a paragraph related to the comparison in an ACS setting at the end of the "Clinical efficacy" section. ***Proposed change*** With respect to arterial thromboembolism, it is recommended to demonstrate efficacy in the setting of an indication such as unstable angina or myocardial infarction without ST	*BMWP-comment:* *Proposal not included and original wording retained.*

	segment elevation. Efficacy assessment should be performed via clinically relevant endpoints. Adjudication of events by a central independent and blinded committee of experts is strongly encouraged. Populations of particular interest should be included: renal impairment, elderly, concomitant antithrombotic therapy (e.g. GPIIb/IIIa inhibitors), invasive intervention (e.g. PCI).	
Section 4.2: Clinical Studies Clinical efficacy **(EGA)**	Notwithstanding our position that clinical efficacy studies should not be required for approval, we have the following comments about the guidelines as written: The equivalence margin is open to diverse interpretation amongst applicants. This could result in approval of different products based on different equivalence criteria. Hence, a clear equivalence margin, based on the required primary efficacy endpoint, should be provided. It should not be so stringent that even different batches of the reference product would have trouble passing against themselves. ***Proposed change*** Large scale Clinical Safety and Efficacy Studies should not be a requirement for approval. In cases where the animal source and the method of synthesis for the product are the same as those for the reference product, and provided that an extensive *in vitro* characterisation comparability exercise supports the "sameness" of the two products, then PK/PD studies in humans (usually patients) should be sufficient. The determination of equivalence margin should be clearly defined. In addition, additional patients should be allowed if the equivalence criteria were not met with the protocol-defined sample size due to an unexpectedly high variability of the data.	*The BMWP comment* *As already mentioned above, we disagree with the proposal to waive a clinical study. From the argumentation given in the guideline, this is not acceptable for biosimilar LMWHs. Equivalence margins should be defined primarily on clinical grounds taking into account information on the reference product and, if applicable, of other LMWH. This is the responsibility of the applicant.*

Studies Clinical efficacy **(EGA)**	The complexity of LMWH results largely from the nature of the starting material, the extraction, the fractionation and the production processes. As minor changes to the process could potentially result in functional changes not detectable in clinical studies, rather, a set of physicochemical methods should be employed, allowing for the exhaustive identification and quantification of any molecular species above a certain threshold. From broad physicochemical characterisation campaigns it is known that for LMWH a threshold of 0.1% prevalence is both technically feasible and sufficient to establish equivalence with the reference product in all attributes of chain composition, distribution, and sequence between originator and biosimilar products. ***Proposed change*** Clinical efficacy studies should not be a requirement for approval, but rather should be waived, provided the applicant can conclusively demonstrate physicochemical comparability,	
Chapter 4.2 Clinical efficacy **(ESC)**	It cannot be claimed that the different measurable pharmacodynamic effects are strictly related to clinical efficacy. Different LMW-Heparins may act similarly in venous thromboembolism but different in arterial embolism. Hence, it is not plausible that if one heparin product proves non inferior to another in DVT or PE it should be regarded equally effective also in arterial embolism. ***Proposed change*** It should instead be mandated that if one product wants to claim equal efficacy to another product already on the market it should give proof of its equal efficacy in both one venous and one arterial thrombotic disorder (e.g. VTE and ACS).	*BMWP-comment:* *In accordance with the concept of biosimilar medicinal products we are of the opinion that for a biosimilar LMWH, provided that convincing similarity on the quality, non-clinical and PK/PD level has been demonstrated, equivalence in terms of efficacy and safety could be shown by one clinical trial, which should be performed in the most sensitive clinical setting. Although differences between VTE and ATE could be discussed the BMWP came to the conclusion that the requirements on pharmaceutical quality, non clinical, PK/PD and clinical level as required in the guideline are sufficient to conclude similarity between the similar and the reference LMWH.*
Chapter 4.2: Clinical efficacy **(ESC)**	No recommendation is given as to arterial thromboembolic disorders ***Proposed change*** Recommendations should be given as to the clinical testing in ACS patients or patients with an AMI (endpoints e.g the surrogate of mortality, stroke & recurrent cardiac event)	BMWP-comment: Proposal not included (see above).

(MB)	The 'surrogate' composite endpoint used in VTE trials is considered acceptable. In this endpoint symptomatic thrombolic events are combined with (a)symptomatic distal DVT as assessed with bilateral venography. This endpoint is more sensitive to pick up differences between products, whereas the clinical relevance has been established for the comparator products primarily on symptomatic VTE. While this approach is considered acceptable, the formulation of 'strongly encouraging' a blinded adjudication and assessment committee this should be a 'sine qua non' in a generic application.	*The BMWP comment:* *We agree and have included this item with the wording:* *Adjudication of VTE events should be performed by a central independent and blinded committee of experts.*
SPECIFIC COMMENTS ON TEXT		
5 CLINICAL STUDIES **CLINICAL SAFETY**		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Clinical safety (page 6) **(EFPIA)**	*Clinical Safety*: Extrapolating the results of one study using a low dose will not provide evidence (safety) for using a high dose and vice a versa. ***Proposed change*** Add safety criteria for the high-dose study. Add safety criteria for bone effects and other know class-specific effects (e.g. osteoporosis/fractures during 6 months of use in the case of dalteparin).	*BMWP-comment:* *Original wording retained.*
Clinical safety 1st § (page 6) **(EFPIA)**	In addition to the size of the prelicensing safety database, it is also important to have a significant proportion of fragile patients. ***Proposed change*** Even if the efficacy is shown to be comparable, the similar biological medicinal product may exhibit a difference in the safety profile. Prelicensing safety data should be obtained in a number of patients sufficient to determine the adverse effect profiles of the test medicinal product. It should also be ensured that a sufficient proportion of fragile patients is included (e.g. elderly, renal impaired, etc.). Care should be given to compare the type, frequency and severity of the adverse reactions between the similar biological medicinal product and the reference products.	*BMWP-comment:* *Original wording retained. Patients with hip fractures are usually elderly, more fragile patients. In addition, not all studies performed with the reference product need to be repeated with the biosimilar (see above), e.g. studies in special populations are not required.*
Clinical safety 2nd§ (page 6) **(EFPIA)**	It is important to confirm that the bleeding risk should not be increased in comparison with the originator product. ***Proposed change*** Usually, comparative safety data from the efficacy trial will be sufficient to provide an	*BMWP-comment:* *Original wording retained.*

	adequate premarketing safety database. Major bleeding events and clinically relevant non-major bleeding events should be carefully assessed and documented. It should be confirmed that the bleeding risk is not increased. A consistent and clinically relevant classification of bleedings should be used. Similar to the efficacy evaluation, the adjudication of bleeding events by a central independent and blinded committee of experts, using pre-specified limits is strongly encouraged.	
Clinical safety (page 6) **(EFPIA)**	Thromboembolism can be the only symptom of HIT. Criterion of drop of thrombocytes is more important than a thrombocytopenia below 100,000/µl. ***Proposed change*** For the detection of immune-mediated type of Heparin-induced Thrombocytopenia (HIT Type II) monitoring of platelet count and an adequate diagnostic procedure in patients developing thrombocytopenia and/or more than a 50% drop of platelets and/or thromboembolism during the trial has to be performed.	*BMWP-comment:* *Proposal included*
Section 4.2: Clinical Studies Clinical safety **(EGA)**	Notwithstanding our position that clinical safety studies should not be required for approval we have the following comments about the guidelines as written***:*** The criteria of equivalent safety profile between products are not specifically mentioned. The requirement for "prelicensing safety data" is stated and the incidence of clinically significant bleeding episodes can be easily monitored. However, if demonstration of similarity in incidence of Heparin-induced Thromocytopenia (HIT) is a requirement, the study sample size would be prohibitive as the incidence is less than 1%. ***Proposed change*** The incidence of adverse events, bleeding events and HIT should not be statistically significantly higher than for the reference product. Given that the mechanism of HIT and the relationship to PF-4 antibody complexation is well understood, we recommend that clinical evidence of similarity on this measure not be a mandatory "pre-licensing" requirement. Rather, *in vitro* data can be provided to demonstrate similarity to the reference product and that incidence of HIT be monitored post-licensing.	*BMWP-comment:* *This comment seems to be a misunderstanding. The guideline does not require to assess comparability of HIT/HITT as a pre-licensing condition. HIT Type II has to be included –as other important rare adverse events like anaphylactoid and anaphylactic reactions in the RMP as reflected by the wording:* *"Within the authorisation procedure the applicant should present a risk management programme/ pharmacovigilance plan in accordance with current EU legislation and pharmacovigilance guidelines. The risk management plan should particularly include rare serious adverse events of the similar biological medicinal product containing LMWH such as Heparin-induced Thrombocytopenia Type II (HIT Type II/HITT, anaphylactoid and anaphylactic reactions.* *Original wording retained, as it indicates that adequate measurements have to be taken granting that patients who develop Heparin-induced—Thrombocytopenia (HIT) during the trial will be adequately identified.* *However, we fully agree that incidence of Heparin-*

		induced Thrombocytopenia (HIT) can only reasonably assessed post-marketing as part of the risk management plan for biosimilar LMWHs..
Section 4.2: Clinical Studies Clinical safety **(EGA)**	The complexity of LMWH results largely from the nature of the starting material, the extraction, the fractionation and the production processes. As minor changes to the process could potentially result in functional changes not detectable in clinical studies, rather, a set of physicochemical methods should be employed, allowing for the exhaustive identification and quantification of any molecular species above a certain threshold. From broad physicochemical characterisation campaigns it is known, that for LMWH a threshold of 0.1% prevalence is both, technically feasible and sufficient to establish equivalence with the reference product in all attributes of chain composition, distribution, and sequence between originator and biosimilar products. ***Proposed change*** Clinical safety studies should not be a requirement for approval, but rather should be waived, provided the applicant can conclusively demonstrate physicochemical comparability,	*BMWP-comment:* *Proposal not included (s. other comments above.)*
Chapter 4.2 Safety **(ESC)**	The relationship between structure, measurable pharmacodynamic effects and different safety aspects (such as bleeding, immunogenicity) are also insufficiently known. ***Proposed change*** Further clinical characterisation (which means a clinical study for the intended indication) of the efficacy and safety for the product claimed to be biosimilar would is also required.	*BMWP-Comment: The BMWP disagrees with these comments. In accordance with the concept of biosimilar medicinal products we are of the opinion that for similar LMWH, provided that comparability on the quality, non-clinical and PK/PD level has been demonstrated, equivalence in terms of efficacy and safety could be shown by one clinical trial, which should be performed in the most sensitive clinical setting. Trials should follow a strict equivalence design where equivalence margins have to be defined a priori by a clinical justification. Although differences between VTE and ATE could be discussed the BMWP came to the conclusion that the requirements on pharmaceutical quality, non clinical, PK/PD and clinical level stated in the guideline are sufficient to conclude similarity between the similar and the reference LMWH. Furthermore the efficacy and safety population is identical in the clinical trial.*

Chapter 4.2 Safety Page 6, para8 **(ESC)**	PF4-heparin antibodies are only relevant, if they in fact do activate platelets. The adequate diagnostic procedure for detection of HIT in patients who develop thrombocytopenia therefore needs to show platelet activation ***Proposed change*** …..and an adequate diagnostic procedure to show not only PF4 heparin complex formation but also platelet activation (e.g. the HIPA) test in patients……	*BMWP-Comment: In our opinion the wording presently proposed for the HIT section is adequate.*
Chapter 4.2 Safety **(ESC)**	The recent issue of contamination by condroitinsulphate hypersolphatate of enoxaparin might be considered ***Proposed change*** More carefully and extensively conducted investigations on non toxicity of LMWH analogues should be considered.	*BMWP-comment:* *(Please refer to the next item for answer.)*
(MB)	Oversulphated-chondroitinsulphate contamination of some raw material has led to serious safety issues and specific requirements pertaining to this should be referred to although this falls outside the scope of the current non-clinical and clinical guideline. This could be addressed in the RMP and a sentence at the end of the clinical safety section is suggested. In addition, follow-up of HITT prevalence should also be given specific attention in the RMP, as due to the rarity of the event it may escape detection in the pre-clinical programme, while an increased risk compared to the innovator product cannot be excluded.	*The BMWP comment:* *Anaphylactoid reactions observed in patients receiving intravenously Heparins have resulted in the identification of OSCS contamination of the raw material for Heparin production. Therefore, now the raw material of all Heparins approved in the EU has to be OSCS free according to the current Ph.Eur.Monographs for Heparin Sodium and Heparin Calcium ((valid since August 2008). However, considering the lection learned from OSCS, anaphylactoid and anaphylactic reactions have been included explicitly in the wording of the Pharmacovigilance section of this guideline. The HIT II issue was already included in the current version of the text sufficiently as a very important point for RMP of biosimilar LMWHs. Additionally we have included the abbreviation HITT (please refer to 4.4).*

SPECIFIC COMMENTS ON TEXT		
6 EXTRAPOLATION OF INDICATION		
Line no. + para no.	**Comment and Rationale**	**Outcome**

Page 7 **(EFPIA)**	Refer to General Comment 3 above. ***Proposed change*** Demonstration of comparable efficacy and safety in surgical patients at high risk for VTE as recommended may allow extrapolation to other <u>venous thrombosis</u> indications of the reference medicinal product if appropriately justified by the applicant. <u>Justification of comparable efficacy and safety in arterial thrombosis indications would require a separate comparative study in the ACS populations.</u>	*BMWP-comment:* *Original wording retained. (see comments above on proposal for two clinical trials item)*
Section 4.3: extrapolation of indication **(EGA)**	Based on the demonstrated *in vitro* and *in vivo* similarity, extrapolation to other indications is appropriate. ***Proposed change*** We recommend removal of "if appropriately justified by the applicant". This statement may be interpreted as requiring something beyond what is the basis of the overarching principle for a comparability exercise.	*The BMWP comment* *We disagree with this comment and do not share the concerns here expressed. Similar recommendations nearly identical in wording can be found in other specific guidelines for biosimilar medicinal products (e.g. Erythropoetin). For biosimilars, extrapolation to other indications is not automatic but has to be justified by the applicant based on sound scientific argumentation.*
Chapter 4.3 **(ESC)**	Different LMW-Heparins may act similarly in venous thromboembolism but different in arterial embolism. Hence, it is not plausible that if one heparin product proves non inferior to another in DVT or PE it should be regarded equally effective also in arterial embolism. Since safety may be markedly different between tow products in the high dose range while they are equally safe in the low dose range. Safety may be a function of time (treatment period/accumulation) ***Proposed change*** No extrapolation to other indications should be allowed (Venous vs arterial wall; VTE prophylaxis vs VTE treatment; ACS vs Embolisms prevention in FA… A single trial in the prevention of VTE in hip replacement is not enough (see above) .A very different background therapy in different indications should be considered bearing in mid a higher risk of bleeding (such as in ACS) It needs to be stated: Extrapolation from equal safety in the low dose range does not allow to extrapolate to equal safety in the high dose range. Hence, equal safety can only	*BMWP-Comment**:** As already mentioned above the BMWP disagrees with these comments. In accordance with the concept of biosimilar medicinal products we are of the opinion that for similar LMWH, provided that comparability on the quality, non-clinical and PK/PD level has been demonstrated, equivalence in terms of efficacy and safety could be shown by one clinical trial, which should be performed in the most sensitive clinical setting. Trials should follow a strict equivalence design where equivalence margins have to be defined a priori by a clinical justification. Although differences between VTE and ATE could be discussed the BMWP came to the conclusion that the requirements on pharmaceutical quality, non clinical, PK/PD and clinical level stated in the guideline are sufficient to derive conclusions on similarity between the similar and the reference LMWH.*

	be claimed if equal safety has been demonstrated in the high range of dosing It needs also be stated: Since different heparins may have different propensity to accumulate in patients with impaired renal function and patients > 75 years, equal safety can only be stated if proven for prolonged treatment periods (>7d) in patients with reduced renal function (clearance 30 – 60 ml/min)-	
SPECIFIC COMMENTS ON TEXT		
7 PHARMACOVIGILANCE PLAN		
Line no. + para no.	**Comment and Rationale**	**Outcome**
(EFPIA)	It should be clarified that rare serious adverse events should be included in the risk management plan even if they have not been reported in the pre-approval clinical database. In addition the incidence and nature of the known class-specific effects should be monitored, especially if long-term use indications are sought. ***Proposed change*** The risk management plan should particularly include rare serious adverse events of the similar biological medicinal product containing LMWH such as Heparin-induced Thrombocytopenia Type II (HIT Type II), even if these events have not been observed in the pre-approval clinical database. Incidence and nature of the known class-specific effects should also be monitored, especially if long-term use indications are sought.	*BMWP-comment:* *Original wording retained.*
Section 4.4: Pharmacovigilance plan **(EGA)**	A Risk Management Plan is the appropriate context in which to address rare adverse events such as Heparin-induced Thrombocytopenia Type II (HIT type II) ***Proposed change*** We recommend removal of comparability of HIT as a prelicensing requirement and monitor it post-licensing (see comments under section 4.2.)	*This comment seems to be a misunderstanding. The guideline does not require to assess comparability of HIT/HITT as a pre-licensing condition. HIT Type II has to be included –as other important rare adverse events like anaphylactoid and anaphylactic reactions - in the RMP as reflected by the wording:* *"Within the authorisation procedure the applicant should present a risk management programme/ pharmacovigilance plan in accordance with current EU legislation and pharmacovigilance guidelines. The risk management plan should particularly include rare serious adverse events of the similar biological medicinal product containing LMWH such as Heparin-*

		induced Thrombocytopenia Type II (HIT Type II/HITT, anaphylactoid and anaphylactic reactions."
SPECIFIC COMMENTS ON TEXT		
REFERENCES		
Line no. + para no.	**Comment and Rationale**	**Outcome**
(EFPIA)	Guideline CHMP/437/04 is into effect since October 2005 and should not be cited as a draft ***Proposed change*** Replace "CHMP/437/04/draft" with "CHMP/437/04"	*BMWP-comment:* *Proposal included.*
(EFPIA)	***Proposed change*** Recommend the addition of the following references to the guideline • CPMP/EWP/707/98 Rev.1 corr – Prophylaxis of High Intra-and Post operative venous thromboembolic risk • CPMP/EWP/6235/04 – Prophylaxis of VTE in non-surgical patients • CPMP/EWP/967/01 – Points to consider on the clinical development of fibrinolytic medicinal products in the treatment of patients with ST segment elevation acute myocardial infarction (STEMI) • CPMP/EWP/570/98 – Points to consider on the clinical investigation of new medicinal products for the treatment of acute coronary syndrome (ACS) without persistent ST-segment elevation • CPMP/EWP/563/98 - Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease • Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues" (EMEA/CHMP/BWP/49348/2005 • Guideline on Immunogenicity Assessment of Biotechnology-derived	*BMWP-comment:* *Proposal included*

	Therapeutic Proteins (CHMP/BMWP/14327/06)	