17 December 2015
EMA/839636/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance (NAS) status of chemical substances' (EMA/CHMP/QWP/104223/2015)

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

Stakeholder no.	Name of organisation or individual
1	European Federation of Pharmaceutical Industries and Associations (EFPIA)
2	European Generic and biosimilar medicines Association (EGA)
3	Gilead Sciences International Ltd.
4	SANOFI
5	Teva Pharmaceuticals

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	**Scope:** Besides esters or ethers, one should consider imines (and oximes) or acetals, which could either come from hydrolysis of an active principle ketone or amine/alcohol (and hydroxylamine). Carbamates, thioesters, carbonates are other examples of potentially hydrolysable moieties that could lead to an already reported active substance. Thus, we suggest replacing: "If the chemical active substance is structurally related as a salt, ester, ether, isomer, mixture of isomers, complex or derivative of an already approved active substance" (lines 77-78) with: "If the chemical active substance is structurally related as a **salt, isomer, mixture of isomers, complex or derivative (such as ester, ether, imine, oxime, carbamate, carbonate, thioester, acetal, etc… or metabolite)** of an already approved active substance." The guidance lacks references to isotopically substituted compounds (e.g. deuterium for hydrogen). This topic would seem to fit naturally into the concepts of this document.	It is not possible to list all potentially hydrolysable moieties that could lead to an already reported active substance. Substances such as imines, oximes, carbamates, carbonates, thioesters, acetals will be considered as derivatives (pro-drugs if after hydrolysis releasing already approved active substances as discussed in the Reflection Paper). The current experience with isotopically *modified* active substances (either "*substituted*" or "*labeled*") is very limited and is too specific to be covered in the Reflection Paper. The QWP will consider publishing additional guidance such as Q&A document on that subject if appropriate.
1	**Regulatory implications**: this paper raised several regulatory questions around CP eligibility, Paediatric submissions … While we appreciate it is not the primary purpose of this document, we would recommend that QWP discusses these further with industry; a 'Regulatory Q&A' could be annexed to the Reflection Paper at a later stage.	The RP provides information on chemical structure and properties criteria that will be considered during evaluation of the NAS claim in the light of article 10.2b of Directive 2001/83/EC. This RP also contains discussion on how applicants can substantiate the NAS claim within the dossier. Other non-technical/scientific considerations are outside the scope of this document.
1	All sections would benefit from examples, like given under 2.3.	Based on the experience gained after finalisation of the RP the QWP will consider either adding examples or publishing

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		additional guidance, e.g. Q&A document.
2	The European Generic and biosimilar medicines Association (EGA) welcomes the publication of the 'Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of New Active Substance (NAS) status of chemical substances' and the message that it gives with regards to the scientific way of approaching the issue of new active substances (NAS) by the competent authorities. The EGA considers it of key importance that the assessment on the NAS status of a substance is robust and agreed at a European level. Moreover the EGA would like to stress that that the assessment of NAS status should be performed during every MAA independent on the legal basis (art. 8(3) or art. 10 of directive 2001/83/EC as amended).	It is emphasised that this RP is intended to provide common guidance to the applicants on how to substantiate the NAS status claim and to the relevant EU competent authorities on how to assess the NAS status claim whenever such claim is made by applicants. This assessment is in the remit of the relevant competent authorities (i.e. EMA for centralised MAAs; National Competent Authorities for national MAAs).
4	When a substance applied exposes the patient to the same therapeutic moiety it is requested to the applicant to provide evidence that the new substance differ significantly in properties with regards to safety and /or efficacy. In the Reflection paper, there is no discussion of situations in which the applied substance has been developed in **an indication different from the one of the previously authorized substance.** In such situations, there is little or no direct comparison of efficacy and safety of the two substances and only nonclinical evidences can be provided in most of the situations. Head to head clinical comparison would not be appropriate since (i) the previous authorized substance is not a suitable comparator (not approved for the new indication and indicated in a different population, subject to specific co-morbidities and co-medications), and (ii) such comparative trials could not be justified by a	The RP describes the chemical structure and properties criteria to be taken into account to qualify a chemical active substance as NAS, as well as the required elements to be submitted by applicants. This RP should be read in conjunction with the "Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance" (Doc. Ref.: EMA/651649/2010) which focusses on the non-clinical and clinical evidence that need to be presented to support the claim that the new substance differs significantly in properties with regards to safety and /or efficacy from the one already approved. Therefore inclusion of additional discussion on non-clinical and clinical requirements to support the NAS claim within this RP is not appropriate and would be out of the scope

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	potential benefit for patients and society (trials would solely be for obtaining the NAS status).	of this document. Applicants are also recommended to seek Scientific Advice if appropriate.
4	It should be clearly defined what is understood as "**therapeutic moiety**" all over the text. Is this referring to the active site(s) of molecules, the pharmacophore ? Please clarify. How will be managed a substance for which the already authorised related substance has no known therapeutic moiety. An evaluation from the Agency of the therapeutic moiety will be required with a written assessment certifying if the therapeutic moiety is new or not. This evaluation will be needed before the company will invest in the development program.	See reply to comment below, lines 145-147 and 178. This RP also serves a guide for applicants and provides information on how the NAS claims could be substantiated in the dossier. This RP should be read in conjunction with the "Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance" (Doc. Ref.: EMA/651649/2010) where further discussion on the non-clinical and clinical evidence that need to be presented to support the claim that the new substance differs significantly in properties with regards to safety and /or efficacy from the one already approved. Applicants may also consider applying for a Scientific Advice if appropriate.
4	In the Reflection paper, it is noted that applicants are advised to seek Scientific Advice to get Agency views about the document to be provided to evidence the differences in terms of safety and/or efficacy when required. It is understood by this mention that Agencies will evaluate the evidence on a case-by-case basis , however i) It is needed to allow a harmonised interpretation across Europe to provide a consistent interpretation and a clear understanding of	This RP should be read in conjunction with the "Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance" (Doc. Ref.: EMA/651649/2010) where further discussion on the non-clinical and clinical evidence that need to be presented to support the claim that the new substance differs significantly in properties

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	what can constitute a "**significant difference in safety and/or efficacy**" to justify that a product is a new active substance. What is the level of evidence to be provided in this case? It can be noted that the Reflection paper EMA/651649/2010 dated 18 Nov 2010 cannot apply to all substances as the "scope of [the] paper [was] restricted to consideration of differences in isomeric composition of a product compared to a racemic reference active substance." ii) It is estimated that a written engagement from Agency of what will and what will not be an evidence of difference in safety and/or efficacy is required for a given substance and should be provided to Companies before engaging in development programs; refusal of NAS affecting the viability of the product.	with regards to safety and /or efficacy from the one already approved. The scope of the above mentioned RP has been revised and extended. The currently published document addresses other types of substances and not only isomers and racemates. Applicants may apply for a Scientific Advice to discuss the particularities of their application, in particular the type of data that would be needed in support of their claim. These Scientific Advices are provided in accordance with the legislation and can not substitute the scientific assessment performed by the relevant competent authorities at the time of the MAA
4	In the Reflection paper, there is no discussion of situations where the same efficacy or safety results from a different mode of action.	As above
4	The designation as a new active substance is critical as this has some regulatory consequences: if not a NAS, the product fall in the same global marketing authorisation as the initial authorisation for data exclusivity purpose. The reflection paper can provide elements about obligations regarding to the paediatric regulations in the case it is the same condition and the same route of administration. If the product is not a NAS, does it still require a full dossier under article 8 or is it possible to provide an abridged dossier?	The intent of this RP is to provide technical information such as describing the chemical structure and properties criteria to be taken into account to qualify a chemical active substance as NAS, as well as the required elements to be submitted by applicants. Inclusion of additional elements concerning obligations in relation the Paediatric Regulation is outside the scope of this document. With regards to the requirements required to establish the quality, efficacy and safety of any substance, this would depend on the particularities of the substance at stake. The extent of the scientific program may be discussed in the context of the Scientific Advice procedure.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
41-45	2	Comment: The Draft reflection paper only refers to article 10.2b of directive 2001/81/EC and chapter 1- Volume 2A of Notice to applicants which may give the impression that the reflection paper is only applicable during applications under article 10. The EGA would like to highlight that the assessment of NAS status will have to be performed for every Marketing Authorisation Application (MAA) independent on the legal basis (art 8(3) or art 10 of directive 2001/83/EC) and using the **same criteria**. Filing under article 8(3) of directive 2001/83/EC as amended should not automatically lead to a NAS status. The EGA would like to highlight that this was partially expressed in the EMA 'Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance'. This Reflection paper did however only cover limited cases compared to the current reflection paper (e.g. ethers and mixtures of isomers were not covered). The EGA would like to stress that the assessment should be applicable to all cases listed in article 10 (2b). Proposed change (if any): Please include that the	A precision has been added in the introductory section that the elements described in the RP are relevant to substantiate a claim of NAS in the context of a marketing authorisation application. The text has been revised accordingly: "This reflection paper intends to provide clarifications for applicants on the elements that needs to be substantiated in relation with a claim of considering an active substance as NAS. Assessment of the NAS status will be performed the light of the principles defined in Article 10.2b of Directive 2001/83/EC and the Chapter I - Volume 2A of Notice to Applicants, as well as the evidence required to substantiate the claim of NAS in a MAA." It is furthermore emphasised that a valid claim of NAS in the context of a marketing authorisation application would be subject to an assessment.

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		assessment of NAS status should be performed during every MAA independent on the legal basis (art. 8(3) or art. 10).	
44-45	1	**Use of Scientific Advice -** lines 44-45: these appear to limit the use of SA to non-listed scenario. We feel however that SA should remain open to cases presented in the paper also, especially where additional data have to be provided to generate evidence of differences in safety and/or efficacy.	Accepted: The scope of Scientific advice is not restricted to the cases not discussed in the RP. The text has been revised accordingly: “However it cannot cover every scenario, and therefore applicants are invited to obtain scientific advice on the studies that may be appropriate to substantiate the NAS claim, especially for scenarios not covered in this reflection paper.”
55-60	4	§ 1.1. Scope In this paragraph it should be mentioned that a new combination of known active substances are excluded from the scope of the Reflection paper as it is not considered to fall within the scope of the global marketing authorisations in accordance with the Notice to Applicant Volume 2A chapter 1 section 5.5. The detailed ground used to consider a product as a new combination should be provided. It should also be mentioned that single ingredient from already authorised fixed combinations are also excluded from this guideline or this specific case should be presented.	Not accepted This is outside the scope of this document which aims to provide technical and scientific information. Applicants may refer to Notice to Applicants Volume 2A Chapter I for further details on combination medicinal products.

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77	4	Please replace: "If the chemical active substance is structurally related as a salt, ester, ether, isomer, mixture of isomers, complex or derivative of an already approved active substance" by "If the chemical active substance is structurally related as **a salt, isomer, mixture of isomers, complex or derivative (such as ester, ether, imine, oxime, carbamate, carbonate, thioester, acetal, etc… or metabolite)** of an already approved active substance." There are other cases besides esters or ethers. One should also consider imines (and oximes) or acetals which could either come from hydrolysis of an active principle ketone or amine/alcohol (and hydroxylamine). Carbamates, thioesters, carbonates are other examples of potentially hydrolysable moieties that could lead to an already reported active substance. Then the sections might be revised in the same order such: 2.1. Salts (in place of 2.6.) 2.2. Isomers (in place of 2.1.) 2.3. Mixtures of isomers (in place of 2.2.)	Not accepted: It is not possible to list all potentially hydrolysable moieties that could lead to an already reported active substance. Substances such as imines, oximes, carbamates, carbonates, thioesters, acetals will be considered as derivatives (pro-drugs if after hydrolysis releasing already approved active substances as discussed in the Reflection Paper).

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		2.4. Complexes (in place of 2.3.) 2.5. Derivatives. The section Esters and ethers (section 2.5.) should also be part of this section. 2.5.1. Prodrugs: esters, ethers, carbamates, thioesters, ect… 2.5.2. Metabolites or metabolic precursors Enzymatic decarboxylation or oxidation could lead to the active substance or the compound might be the active metabolite of a previously reported active principle.	
85-89	1	2.1. Isomers – Lines 85-99: this section should include specific Rotamers also, such as Atropoisomers (stereoisomers arising because of hindered rotation about a single bond), and which can exist as pure isomers or as a mixture of isomers.	Not accepted: Chirality is an inherent property of a molecule that is only related to the symmetry. Only as long as any form of a molecule that lack an improper axis of symmetry S_n cannot convert to a form with a higher symmetry it is chiral. Whether the barrier to convert to a form of higher symmetry is the hindered rotation around a single bond or breaking/forming of covalent bonds has no impact. Atropisomers are therefore fully covered by the present wording interpreting isomers as enantiomers (of chiral substances).
93-94	2	Comment: The EGA would like to highlight that the reflection paper does not specify how significant a difference between safety and efficacy must be in order to justify NAS status of	Not accepted: The RP describes the chemical structure and properties criteria to be taken into account to qualify a chemical

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		a substance. (e.g. changes in pharmacokinetics alone should not justify NAS status). The justification/assessment should be considered a part of the assessment report and should be made publicly available through PAR/EPAR in order to harmonise the interpretation of factors justifying NAS status of a substance.	active substance as NAS, as well as the required elements to be submitted by applicants. This RP should be read in conjunction with the "Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance" (Doc. Ref.: EMA/651649/2010) which focusses on the non-clinical and clinical evidence that need to be presented to support the claim that the new substance differs significantly in properties with regards to safety and /or efficacy from the one already approved. Therefore inclusion of additional discussion on non-clinical and clinical requirements to support the NAS claim within this RP is not appropriate and would be out of the scope of this document. Whenever relevant, the discussion about the NAS claim is included in the EPAR which is publically available on the EMA website.
95-96	4	§2.1. Isomers Does it include Atropoisomers, that are specific rotamers (ie Atropoisomers are stereoisomers arising because of hindered rotation about a single bond). If not already included, we propose to add this kind of	Please note the answer to the comment for lines 85-89

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		isomers. These isomers can exist as pure isomers or as a mixture of isomers.	
104-105	2	Same comment as for line 93-94	Please note the answer to the comment for lines 93-94
110-111	3	Comment: The term “complex” is used in the literature to refer to a wide range of structures including solvate, hydrates, and cocrystals. Section 2.3 appears to address two specific types of complexes. The introduction of the section could be clarified to indicate that only a subset of complex types are being discussed in this section. Proposed change (if any): The term ‘complexes’ ~~encompasses several types of~~ may be used to refer to a wide variety of structures. ~~Two~~ The potential for NAS designation for two specific ~~examples~~ types of complexes used as medicinal products for human use ~~can be found~~ is discussed below.	Accepted The text has been revised as follows: The term ‘complexes’ may be used to refer to a wide variety of structures. Two categories of complexes used as medicinal products for human use are discussed below.
122-123	2	Same comment as for line 93-94	Please note the answer to the comment for lines 93-94
133	4	§2.4. Derivative In order to clarify the word Prodrug, we propose to exemplify it as it is done in the &2-5 (line 145). Esters and Ethers are a subgroup of derivatives. Some examples could be provided according to chemical family (ester, ethers, disulfides, …)	Not accepted: Please see reply above in general comment.

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		and purpose as improvement of ADME (bioavailability, in vivo distribution), stability, …	
142	5	Proposed change (if any): add after line 142: "In an analogous situation to a racemate and an active enantiomer, a product should not be considered a new active substance where it was previously authorised in combination with an inactive substance and the inactive substance has now been removed in the new product. This is because the active moiety is the same in both products – all that has been removed is an inactive component. In this sense "inactive" and "active" need to be assessed on the basis of the presence or absence of clinically relevant pharmaceutical activity in the context of the medicinal product in question."	Rejected These regulatory considerations are outside the scope of this document which is intended to provide technical and scientific recommendations in the context of substantiating a claim of NAS. Applicants may refer to Notice to Applicants Volume 2A Chapter I for further details.
145-147 and 178	1	**Therapeutic moiety**: we understand from lines 145-147 and 178 that this refers to the actual chemical moiety (patient exposure), and not the pharmacopohore; it would be helpful to have this defined from the start of section 2 also.	The term therapeutic moiety does not refer to the pharmacopohore. The text in section 2 has been revised as follows: Such substance is considered to be new in itself, when the administration of the applied active substance would not expose patients to the same therapeutic moiety as already authorised active substance(s) in the European Union.
149-151	2	Same comment as for line 93-94	Please note the answer to the comment for lines 93-94

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
161-163	2	Same comment as for line 93-94	Please note the answer to the comment for lines 93-94
167-169	2	Same comment as for line 93-94	Please note the answer to the comment for lines 93-94
170	3	Comment: Section 2.7 is ambiguous about the potential status of polymorphic forms. Lines 167-169 discuss that salts could have NAS status with adequate safety and/or efficacy justification. Polymorphic forms are discussed immediately after this with a statement beginning “This applies also...” Does the exception that NAS status could be given for a different salt form with adequate safety and efficacy justification also apply to polymorphic forms? If alternate polymorphic forms would never be considered as NAS the section could be clarified by removal of the sentence “This applies also to morphologically different crystals forms of an active substance.”	Comment noted The text has been revised accordingly: ~~“This applies also to~~ Regarding the ~~morphologically different crystal forms~~ different crystalline polymorphs of an active substance, in principle the differences between such polymorphic forms will immediately disappear when dissolved and ~~they~~ therefore will be presumed ~~considered~~ as the same active substance.” In principle it cannot be excluded that the NAS status could be given to different polymorphic forms if adequate safety and/or efficacy justification is provided. It is therefore appropriate to keep the statement on polymorphs.
170-172	3	Comment: This section combines two separate concepts: morphology (external crystal shape) and polymorphism (arrangement of molecules in the crystalline lattice). Polymorphism is the more important of these topics and the text should be clarified to refer to polymorphism specifically.	Accepted The text has been revised as follows: ~~“This applies also to~~ Regarding the ~~morphologically different crystal forms~~ different crystalline polymorphs of an active substance, in principle the differences between such polymorphic forms will immediately disappear when dissolved and ~~they~~ therefore will be presumed ~~considered~~

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): This applies also to ~~morphologically different crystal forms~~ different crystalline polymorphs of an active substance. The differences between such polymorphic forms will immediately disappear when dissolved and they will be considered as the same active substances.	as the same active substance.”
174-177	2	Same comment as for line 93-94	Please note the answer to the comment for lines 93-94