EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2012
EMA/355542/2011

Overview of comments received on 'Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer) as new active substance in relation to a reference active substance which is a racemic mixture of enantiomers' (EMA/651649/2010)

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

Stakeholder no.	Name of organisation or individual
1	Norgine Limited
2	EFPIA = European Federation of Pharmaceutical Industries and Associations
3	Sunovion Pharmaceuticals Inc (formerly Sepracor)
4	H. Lundbeck A/S
5	The Medicines Evaluation Board in the Netherlands
6	EGA = European Generic medicines Association
7	ECNP = European College of Neuropsychopharmacology
8	Pfizer Inc

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	The title text “in relation to a reference active substance”: does this mean **reference medicinal product** as defined in Article 10 of 2001/83/EC? We would request confirmation that if different salts, esters, ethers, isomers, mixture of isomers, complexes or derivatives of an active substance are subject to complete development, and do not rely on previous findings of safety and efficacy of a reference medicinal product containing the precedent NAS, then these different molecules could be considered to be a NAS and the medicinal product application would be submitted under Article 8 of Directive 2001/83/EC. In this case, we would consider that head to head clinical trials would not be required. However, if the scope is to rely on the data of the reference medicinal product of the racemate, then head to head clinical trials could be required	Consideration of an active substance as new active substance is not dependent on whether it was subject to a complete development or not, but on whether the enantiomer, complex, derivative, different salt or ester differs significantly in properties with regard to safety and/or efficacy vis-à-vis the racemate. An active substance may be subject to a complete development and not be considered as a new active substance. Reference is made to Article 10.2(b) of Directive 2001/83/EC, i.e. *‘different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance unless they differ significantly in properties with regard to safety and/or efficacy.’*
2	This consultation document, although carefully constructed and aiming to clarify some important issues, has a number of fundamental weaknesses which are discussed below.	

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	CHMP's proposed reflection paper concerns a test for NAS status in the context of regulatory data protection and other important legal rights and obligations connected to the Global Marketing Authorisation concept. The definition of NAS is a legal question or at the very least a part legal and part scientific question. It is, therefore, open to debate whether, in the first instance, it is appropriate for the CHMP, in its role as scientific advisory body, to develop guidance on this topic at this time. The definition of a New Active Substance for the purposes of the legislation is a critical one from many perspectives and should not be determined, expressly or by implication, by the CHMP in the context of a paper relating to racemates and isomers. <u>Other important points to be considered include:</u> <u>Construction of the reflection paper does not recognize the historical context</u>. In 2004, Article 10 of Directive 2001/83 was amended to include the definition of a 'generic medicinal product' and how to interpret in this context the different salts, esters, ethers, isomers etc. The EU Commission maintains that the amendments reflected what was in the Notice to Applicants and other guidance (including the Chirality Guideline). An investigation of historical regulatory practice in the 1990s and thereafter confirms that the definition of NAS was indeed interpreted differently to the current interpretation proposed in the draft reflection paper. The definition in the reflection paper	Reference is made to *The procedure for European union guidelines and related documents within the pharmaceutical legislative framework (EMEA/P/24143/2004 Rev.1 corr)*, where it is explained that a reflection paper may be developed to communicate the current status of discussions and can provide a framework for discussion or clarification particularly in areas where scientific knowledge is fast evolving or experience is limited. It is also acknowledged that a reflection paper does not provide scientific, technical or regulatory guidance, but may contribute to future development of such guidelines or related documents.

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	requires that NAS status must be proven to exist and requires demonstration of a clinically significant difference in either safety and/or efficacy between racemate and a single isomer usually via head-to-head randomised clinical studies in the same indication. No prior guidance has suggested this to be required and a different approach was consistently taken by regulators and industry.	The reflection paper has been revised to take into account this comment.
	Scope of guidance: There is no justification for separately addressing single isomers. The definition of a New Active Substance in the Notice to Applicants is not limited to isomers and also comprises salts, ethers, complexes and derivatives as well as a biological substance differing in molecular structure or a new salt. The reflection paper should clearly address these other forms and indicate whether or not the same principles apply. We propose in this regard that biologicals are explicitly excluded from the scope of this guidance with reference to related guidelines describing the comparability requirements for biologicals.	The scope of the reflection paper has been revised to include the other forms referred to in Article 10.2(b) of Directive 2001/83/EC. Agreement to exclude biologicals from the scope of the reflection paper.
	Ethical Considerations: The paper does not address the practical/ethical issues that will arise on clinical testing. New products are normally tested against placebo or existing active compounds and companies are encouraged to test against the current best/standard therapy. The CHMP's requirement for head-to-head studies against the racemate will raise serious questions about the ethical justification for this, if the racemate is no longer the standard therapy or indeed	There is no requirement for head-to-head studies against the racemate for approval of an enantiomer. This requirement may only be applicable when the Applicant claims that the enantiomer should be considered as a new active substance vis-à-vis the racemate, i.e. that it differs significantly in properties with regard to safety and/or

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	where the new active substance is being developed for a new indication and the racemate was never authorised for that indication. The CHMP concedes that the data may not be required for licensing (i.e. for public health reasons requiring proof of the efficacy and safety of the new product) and it is therefore questionable whether the proposed approach is in all situations feasible from an ethical point of view. Our detailed comments provided on the CHMP text should not be taken as accepting that the existence of significant and clinically relevant differences represents the only or most appropriate way of defining a NAS in the context of regulatory approval of new products.	efficacy. The reflection paper has been revised to take into account this comment.
3	The draft Reflection Paper ("the Paper") rightly recognises that where a concept such as New Active Substance ("NAS") has such potentially important regulatory implications, including for data protection, there should be clarity as to the meaning of that concept and the evidence required to demonstrate that the test applicable has been met. As a company with a strong research interest in single isomers, we support the aim described in the Paper of ensuring that companies have a clear understanding of what will and will not constitute a NAS so that this can be taken into account when designing development programmes that are inevitably already extremely costly. Our comments below are in part informed by our experience between 2007 and 2009 in seeking authorisation in the EU for our product	

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	Lunivia (eszopiclone)[1]. The position adopted by the EMA/CHMP to the assessment of Lunivia and its status as a NAS was not something we could reasonably have anticipated from prevailing guidance or discussion with regulators prior to submitting our centralised application for the product. The Paper additionally notes the relevance of these issues for determining access to the centralised procedure and our experience also supports this point, because the approach adopted by the EMA and described in the Paper creates considerable difficulties for companies and regulators as it results in a situation where eligibility for an extended and costly procedure cannot finally be determined until the procedure is complete! The Paper also suggests that it merely aims to "harmonise" the approach to the interpretation of the legislation and guidance. It does so as if it was reciting and explaining an established approach to the proper interpretation of the concept of NAS, and the data required to meet the test of NAS, which merely needed to be made more transparent. We respectfully believe this not to be the case. The proposed approach is inconsistent with an objective view of the language used to define NAS status in the Notice to Applicants, the original purpose of this definition, the reference to the application of the concept in both general and product specific guidance prior to this Paper and its practical application in the past by both industry and	The outcome of the scientific assessment on whether a single enantiomer or other form is to be considered as a new active substance compared to the reference active substance has no impact on a previously granted access to the centralised procedure.

[1] *The dispute to which this gave rise is still the subject of a claim before the General Court.*

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	regulators. This is important because if, as we contend, the approach adopted in the case of Lunivia (and which is now reflected in the Paper) constitutes a new approach, it is plain that a piecemeal approach to defining NAS of this type, initially involving consideration of single isomers alone, is not appropriate. A definition of the regulatory test and the evidential aspects should be examined comprehensively and in the context of all relevant product types to ensure a coherent and principled approach. Moreover, there are important questions as to whether the EMA or its scientific advisory body is properly empowered to develop definitions in such a context. **<u>The Paper represents a change of approach</u>** The Paper accurately describes the definition contained in Annex III to Chapter 1 of the Notice to Applicants ("NTA") and the language of Article 10.2(b) of Directive 2001/83 that addressed one of the categories of NAS using similar language. However, there is nothing to support the suggestion that the legislation or guidance has been viewed as justifying an interpretation of NAS that requires "clinically relevant human/safety and/or efficacy differences" as demonstrated by the results of head-to-head randomised clinical trials between racemate and single isomer.	The scope of the reflection paper has been revised to include the other forms referred to in Article 10.2(b) of Directive 2001/83/EC. With regard to whether the EMA or the CHMP is properly empowered to develop definitions in such a context, reference is made to Chapter 1 of Volume 2A of the Notice to Applicant where it is stated that the decision whether a different form of the active substance is to be regarded as a new active substance should be taken by the competent authorities on a case-by-case basis.

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	We would make the following points: • Language of the NTA: The language of the NTA for all of the product types (and the language of Article 10.2(b) which the Commission has said merely reflected the NTA) does not import any principle that the results of the testing of the new product (which is justified by the different properties of the active substance) must demonstrate a significant and clinically relevant difference between the new product and the original product before the test of NAS would be treated as met. It would have been easy to capture in simple language that concept, if that had been the intention. Instead the focus was upon whether a change in the characteristics or properties relevant to the safety and/or efficacy of the new product meant that the product's efficacy and safety required new research data for assessment. Therefore where any changes in the properties of a single isomer (commonly treated as referring to its pharmacokinetics, pharma-dynamics, and toxicity) were sufficiently significant that they could change the efficacy/safety profile of the product, the NTA required that the product must be treated as a NAS for regulatory purposes. The references to changes in biological products and radiopharmaceuticals sufficient to qualify them as NAS all contain no hint that the changes must also lead to a clinically significant difference in safety or efficacy compared with the related products before NAS status on the basis of "added clinical value" would be	The aim of the reflection paper is to have a harmonised approach on the interpretation of what constitutes a significant difference with regard to safety and/or efficacy and the level of evidence required to confirm designation of an enantiomer, complex, derivative, different salt or ester as a new active substance vis-à-vis the reference active substance. The reference to clinically relevant human safety and/or efficacy differences should not be understood as requiring "added clinical value"

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	accepted. • Language of the Annex to the Directive: The only relevant reference to the principle of NAS in the Directive appears in Paragraph 3 of Part II of the Annex to the Directive which uses language inconsistent with the definition of NAS contained in the Paper. It refers to the need to treat an active substance as a NAS even where it has the same therapeutic moiety as the original product if it contains a different salt/ester, complex/derivative and there is a change in the pharmaco-kinetics of the moiety, pharmacodynamics and/or in toxicity "which could change the safety/efficacy profile" (emphasis added). It does not refer to a change in properties which on testing "have been demonstrated to result in, clinically meaningful differences in safety or efficacy". Similar language is used in Annex IV to the NTA which requires the authority to consider whether there is any "change in the pharmacokinetics of the moiety, pharmaco-dynamics and/or in toxicity which could change the safety/efficacy profile (otherwise to be considered as a new active substance)" (emphasis added). It is significant that the statement in the Directive's Annex was included by the Commission in 2003 in the context of the application of the abridged procedures and data protection concerning differences in salts between two products. If the definition of NAS contained in the Paper is to apply, it would appear that this provision in the Annex would be misleading and would require legislative amendment.	The Annex to the Directive 2001/83/EC was last amended by Directive 2003/63/EC of 25 June 2003 while the reference to the fact that different salts, esters, ethers, isomers, mixture of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance unless they differ significantly with regard to safety and/or efficacy was included in Directive 2001/83/EC by Directive 2004/27/EC of 31 March 2004.

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	Amendment would also be required to Annex IV. • Original purpose of NTA definition: The interpretation of the NTA suggested by the Paper is inconsistent with the original purpose of the definition and makes its use as an eligibility criterion for centralised assessment unworkable. The definition of NAS in the NTA was developed 20 years ago for the purpose of defining products whose active substance(s) were sufficiently different to be eligible for a harmonised central assessment because they had to be treated for regulatory purposes as containing a NAS. An assessment of properties different enough to require a new data package can readily be applied as an eligibility test: the definition in the Paper of NAS presupposes a detailed and complex assessment that cannot • Prevailing guidance: Past and current guidance on the development of single isomers, notably the Chirality Guideline, is based upon the principle that products containing single isomers should be treated as containing a NAS and tested as such. Consistent with this single isomers have been given separate INNs. We believe it instructive that none of the representatives of national authorities whom Sunovion (formerly Sepracor) consulted in 2006 and who sought to provide helpful comments on the eligibility of Lunivia for centralised assessment as a NAS ever suggested that the test of NAS was, in fact, as now described in the Paper. Nor did this suggest that 'head to head' controlled clinical trials between racemate and single	The eligibility to the centralised procedure is not put into question, i.e. if the reference active substance was subject to centralised procedure, the enantiomer or other form will also be eligible, but will be considered to be the same active substance, unless there is a claim by the Applicant of a significant difference in properties with regard to the safety and/or efficacy vis-à-vis the reference active substance. Amendments have been proposed to address this comment

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	isomer were required, although it was plain from the summary information provided that the core trials conducted by Sunovion were adequate and well-controlled long term trials with placebo controls only. Past approval practice: The Head of Agencies website shows that from the mid-1990s several major products based upon single isomers and approved, through mutual recognition procedures, following publication of the current edition of the Chirality Guideline, were classified as containing a NAS. This is despite the fact that the literature contains no reference to the availability of controlled clinical trials comparing racemate and single isomer of the type now said by the Paper to be the normal way of demonstrating that the test of NAS has been met. This is not consistent with the idea that the guidance contained in the Paper represents the accepted approach and was generally applied in industry or regulatory circles.	in section 2.2 of the reflection paper. Directive 2004/27/EC of 31 March 2004 which has amended Directive 2001/83/EC has clarified, in Article 10.2(b) that the different salts, esters, ethers, isomers, mixture of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance unless they differ significantly in properties with regard to safety and/or efficacy. The scope of the reflection paper is to give guidance on the level of evidence that would be expected to demonstrate that the enantiomer or other forms differs significantly in properties with regard to safety and/or efficacy vis-à-vis the reference active substance.
4	Lundbeck welcomes the opportunity to provide its position on this draft reflection paper. In general, it is difficult to fully understand the context and rationale for the publication of this paper as well as the standards it sets around NAS status for single enantiomers. Also some statements lack	

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	precision and a lot seem to be left open to judgement. It raises a number of concerns, including: **Legislation is necessary: Commission rather than the CHMP through scientific guidance should lead on the legal test** - The draft reflection paper provides that two separates development tracks may be required: one for licensing and one for determination of a substance as a NAS, based on different tests and different data requirements. Currently there is no legal basis in Directive 2001/83/EC and/or Regulation EC/726/2004 for the requirement to perform a separate and additional test for the designation of NAS status and determining regulatory data protection. Likewise, a requirement to perform a head-to-head study in order to prove NAS status is new and not included in the Annex to Directive 2001/83/EC. If a change of policy is required this new policy and the requirements involved should be set by the legislator rather than through an advisory body like the CHMP. - As the designation of a substance as a NAS determines regulatory data protection the relationship with the concept of global marketing authorisation should be explained and anchored in the law to ensure	It is confirmed that there is no legal requirement to perform additional test for the designation of NAS status. The regulatory consequence is that, as provided for in Directive 2001/83/EC, the active substance will be considered to be the same as the relevant reference active substance. The requirements set out in the reflection paper concern the level of evidence that would be expected to demonstrate that the active substance differs significantly in properties with regard to safety and/or efficacy vis-à-vis the reference active substance, should the Applicant claim NAS. The assessment of NAS status is of a scientific nature and should be performed by the CHMP or National Competent Authority in the framework of assessment of an application

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	legal certainty. - It is proposed that decisions on NAS designation are agreed at either the CHMP or the CMD(h). As NAS status determines the legal concept of regulatory data protection, the tasks and the responsibilities of the CHMP and the CMD(h) should be explained and need a legal basis. - The draft reflection paper reverses the baseline assumption that the development of a single enantiomer concerns the development of a NAS laid down in the note for guidance on the "INVESTIGATION OF CHIRAL ACTIVE SUBSTANCES" (3CC29a). The relationship between the two documents should be explained. **Scope of the paper** - The draft reflection paper addresses only one category of the definition of NAS in the Notice to Applicants and only the case of single enantiomers within this category. A justification for this selection is not provided. The designation of single enantiomers as a NAS should be looked at and explained in the context of the other parts of the definition of NAS. E.g. in respect of biologicals changes in molecular structure, nature of source material and the manufacturing process provides NAS status. These changes mean that new studies are required in order to obtain a marketing authorisation but they rarely change the safety/efficacy profile of a product. The Chirality Guideline is based on the same principle, i.e. that from a scientific perspective it is not safe to extrapolate the data developed for the racemate to the	for marketing authorisation. The scope of the reflection paper has been revised to include the other forms referred to in Article 10.2(b) of Directive 2001/83/EC. Directive 2004/27/EC of 31 March 2004 which has amended Directive 2001/83/EC has clarified, in Article 10.2(b) that the different salts, esters, ethers, isomers, mixture of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance unless they differ significantly in properties with regard to safety and/or efficacy.

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	single enantiomer. **History** - The paper does not recognise that in respect of providing NAS status neither the law nor existing guidance have changed. Furthermore, in previous applications in the nineties and onwards, products have been classified as a NAS based on a different regulatory practice, procedure and assessment than is proposed in the draft reflection paper. More specifically the interpretation/requirement that clinically relevant differences should be shown through head to head studies comparing the single enantiomer with the racemate in order to obtain NAS status was not recognised nor imposed. It should be clarified that if there is a case for change it should be addressed in legislation and it cannot have a retroactive effect on NAS designation of single enantiomers in the past. **Justifying the research** - If head-to-head becomes the requirement to obtain NAS status, it significantly increases the number of patients to be included in the clinical trials and hence the duration and burden of evidence so as to effectively prevent the development of such compounds. - It is unethical and not in the interest of public health to significantly increase the number of patients to be exposed to experimental medicinal products for the sole purpose of designation of NAS status.	The reflection paper gives guidance on the level of evidence that would be expected to demonstrate that the active substance differs significantly in properties with regard to safety and/or efficacy vis-à-vis the reference active substance, under the current legal framework. Amendments have been proposed to address the requirement for head to head studies in section 2.2 of the reflection paper. There is no retroactive effect of the reflection paper on previous NAS designations of single enantiomers. The evaluation of what constitutes a new active substance is of a scientific nature and should be performed by the CHMP or the National Competent Authority in the framework of assessment of an application for marketing authorisation. There is no requirement for head-to-head studies against the racemate for approval of an enantiomer or other forms. This requirement may only be applicable when the Applicant claims that the enantiomer or other form should be considered as a new active substance vis-à-vis the reference active substance, i.e. that it differs significantly in properties

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	Furthermore, with respect to licensing, studies are conducted against placebo or the best standard available. If the racemate is no longer considered to be the best standard available a comparative test between the single enantiomer and the previous approved racemate, without medical justification, is no longer acceptable. This is even more difficult if the single isomer is tested for another indications (patient population) than that approved for the racemate. Furthermore, given the interest to show difference from isomers, one could wonder if a similar eagerness to document "non-difference" from new formulation/generics is not equally warranted. Additionally, some of the benefits associated with isomers may not lend themselves well to investigation in a clinical trial setting (e.g. improved safety or other benefits). - There are a number of inconsistencies within the draft paper where it requires head-to-head trials and then provides examples where such approach may not be appropriate. Example of this are provided in the specific comments section. - The definition of what is clinically relevant is still unclear and is more or less open for judgement. Our overall position is that if the principles set out in this draft	with regard to safety and/or efficacy. The default position provided for in Article 10.2(b) of Directive 2001/83/EC is that the different isomers shall be considered to be the same active substance unless they differ significantly with regard to safety and/or efficacy. It is up to the Applicant to decide if they wish to pursue the NAS claim, as this is not a regulatory requirement for approval. The reflection paper has been revised to take into account this comment. The onus remains with the applicant to justify that there are significant differences in safety and or efficacy. These should be more than theoretical.

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	reflection paper are applied, they would hamper innovation.	
5	None	
6	The European Generic medicine Association (EGA) welcomes the publication of this important document. We only regret that the paper has been published relatively late. Earlier publication would have helped to avoid lengthy discussions at the moment of validation of generic applications and some unnecessary litigation, had the similar interpretation been extended to already granted Marketing Authorisations. Nevertheless the Reflection Paper gives a very clear message of the future scientific way of approaching the issue of new active substances by the Competent Authorities also in the case of other types of differences than enantiomer/ racemate. The clear conclusion and justification as to whether the substance is considered as a new (NAS) or not, should routinely be a part of the EPAP/ PAR published by the Competent authorities at the end of the MA process.	The conclusion on whether a substance is considered as a new active substance will be part of the EPAR.
7	The group which considered this document felt that it was timely and much-needed and generally satisfactory. However there were some areas where it might be amended, to clarify potential ambiguities and to enhance its potential impact.	

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	The document is rather short and although this is commendable, it might be improved by the inclusion of more detail and some illustrative examples. We felt that some basic principles should be enunciated at the beginning of the statement, and that the default position should be to support enantiomer development providing this leads to improved efficacy or tolerability, rather than to inhibit their development. We were unclear why licensing rules for enantiomers should be different from other NAS rules. The requirements for enantiomers appear to be more extreme than those for other drugs which is not logical. Specifically, there is a requirement for evidence of increased safety and/or efficacy in clinical samples for applications for enantiomers, when compared with racemic mixtures. This requirement, for demonstration of superiority, is not stipulated for other drugs with similar pharmacological properties. A clearer statement of why this should be the case for enantiomers is needed. Would this stipulation for demonstrating the superiority of enantiomers in clinical samples still be needed, if the enantiomer has already clearly shown that it possessed important differences from the racemate, in pre-clinical tests? We also contend that if an enantiomer is significantly different from	Amendment proposed to reflect this comment. The licensing rules for enantiomers are not different from any other active substance neither is there any requirement for evidence of increased safety and/or efficacy for applications for enantiomers when compared with racemix mixtures. The requirement for additional data is only applicable when the Applicant claims that the enantiomer or other forms should be considered as a new active substance vis-à-vis the reference active substance, i.e. that it differs significantly in properties with regard to safety and/or efficacy.

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	the racemic mixture in its preclinical pharmacological properties, then it is a different functional entity, whether or not clinical distinctions can be found. With the current position, it implies it would be harder to develop an enantiomer of - for example - an SSRI than it would be to develop yet another SSRI of different chemical structure but more similar pharmacology, as the package for the enantiomer would need to include a demonstration of superiority, whereas the package for the other drug would not need to do this. This seems curious. It was helpful to have examples of what might constitute meaningful differences in toxicology as being acceptable for recognition with NAS status, but surely the key issue that is currently overlooked is that of what constitutes a pharmacologically meaningful difference. The principal challenge is to define how great a difference in pharmacological properties is required for award of NAS status. We feel that the inclusion of some illustrative examples here would be most helpful, but if there are none then there would be a need for some statement such as .. ."biological effects of significant magnitude to be predicted to be clinically meaningful should be considered as relevant .... for example, a two-fold difference in effect at a meaningful pharmacological target". The ECNP would be prepared to help with the process of defining these new criteria in a revised version of this statement.	See clarification above. A pharmacologically meaningful difference should translate into significant differences in properties with regard to safety and/or efficacy. The issue relates to designation as a NAS, not to marketing authorisation requirements. A pharmacologically meaningful difference demonstrated in animals that does not translate into safety or efficacy differences would not constitute adequate evidence for designation as NAS

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8	This Reflection Paper (EMA/651649/2010 dated 18 November 2010) describes considerations for distinguishing isomeric composition of a biopharmaceutical product compared to a racemic reference active substance. Two basic categories of considerations are addressed: (a) Criteria for classifying an enantiomer as a New Active Substance (NAS) and (b) The level of evidence required to confirm the designation of an enantiomer as a NAS. We appreciate the EMA and CHMP's decision to make this Reflection Paper available for public consultation prior to its finalization and adoption by the CHMP. Overall, it appears that the purpose of the document is to clarify the requirements for designation of an enantiomer as a NAS. This is inexorably linked to biopharmaceutical innovation and has global implications. The document deals with important legal issues impacting on the innovator's rights and exclusivity, as well as scientific issues, and also indirectly underscores the importance of public-private cooperation in effectively advancing innovation and the associated need for strong intellectual property protection. We strongly support innovation in the discovery and development of biopharmaceutical products for the benefit of patients and promotion of the public health. The document remains silent on the specific process and hierarchy of evidence to be used to designate an enantiomer as a NAS. A more transparent process could serve to facilitate harmonised agreements	

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	at a European level, e.g., across products handled through centralised, national, mutual recognition, or decentralised procedures. We appreciate the opportunity to participate in the public consultation process; we would be glad to meet with EMA representatives to clarify any of our comments.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
	7	There were a number of areas where the phrasing might be improved, in order to reduce potential ambiguity and enhance the overall impact.	
	7	For example, the phrase in 2.3 “extrapolation between studies” is difficult to understand. Does this mean extrapolation from studies about superior efficacy? If so, would this include the findings of meta-analysis?	This has been clarified in the reflection paper.
Section 1	**1**	**Proposed change** “The scope of this paper is restricted to consideration of differences in ~~isomeric~~ enantiomeric composition” **Comment** Reference active substance: does this mean reference medicinal product	Reference active substance refers to the active substance to which the ‘new’ active substance compares as e.g. a derivative, complex, a different salt, ester, isomer or mixture of isomers.
Section 1	**2**	**Comment:** [Critical] It is indicated that the scope of the paper is "restricted to consideration of differences in isomeric composition of a product compared to a racemic reference active substance". Yet, as is obvious from the 4 bullet points, the definition of a New Active Substance in the Notice to Applicants is not limited to isomers and also comprises e.g. a biological substance differing in molecular structure or a new salt. The reflection paper	The scope of the reflection paper has been extended to include the other forms referred to in Article 10.2(b) of Directive 2001/83/EC.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		should clearly address these other forms and indicate whether or not the same principles apply. We propose in this regard that biologicals are explicitly excluded from the scope of this guidance with reference to related guidelines describing the comparability requirements for biologicals. In addition, it should be clarified how this reflection paper relates to the recommendations in the Guideline on the Investigation of Chiral Active Substances (3CC29a) **Proposed change (if any):**	Agreement to exclude biologicals from the scope of the reflection paper.
Section 1	**3**	**<u>A comprehensive approach is required</u>** **Comment:** The Paper notes that the only definition of NAS is contained in guidance currently set out in Annex III to Chapter 1 of the NTA. The NTA provides a definition of NAS by reference to the various types of product where the definition is relevant. The NTA describes the four categories as being substances not previously authorised as a medicinal product in the EU; isomers, derivatives, salts etc of previously authorised products; biological substances previously authorised but differing in molecular structure, nature of source material or manufacturing process; and radiopharmaceutical substances where the radionuclide or ligand or coupling mechanism has not previously been authorised. In our	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		view it is important that the principles underlying the test of NAS and the evidence required to show the test is met are not developed by reference to one category only - single isomers. Such an approach can predispose to arbitrary distinctions and unjustified discrimination between products in different classes. The definition of the test and the evidential aspects should be examined comprehensively and in the context of all relevant product types to ensure a coherent and consistent approach with any justified distinctions being properly explained.	The scope of the reflection paper has been extended to include the other forms referred to in Article 10.2(b) of Directive 2001/83/EC.
1. Introduction	**7**	Proposed change: The scope of this paper is restricted to consideration of differences between a single enantiomer product and the corresponding racemic reference active substance. The question being addressed is "when should an enantiomer be regarded as a new active substance (NAS) in relation to the relevant racemic reference active substance and what level of evidence would be required to justify the designation as a new active substance. The current legislation….	The scope of the reflection paper has been extended to include the other forms referred to in Article 10.2(b) of Directive 2001/83/EC.
2. Discussion	**7**	Proposed change: Designation as a new active substance is critical as this has regulatory consequences. With a designation as a new active substance the single enantiomer medicinal product will not be part of the same global marketing authorisation as the initial authorisation for the racemic mixture and	Regulatory consequences of designation as new active substance have been removed from the reflection paper, as these stem from the legislation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		will differ for data exclusivity purposes.	
Pg 2, Sect 2 (Discussion)	**8**	**Comment:** We recognize that historically the majority of single isomer situations presented to regulators involved cases in which one of the isomers is apparently biologically inert and the single isomer being developed is the active isomer. This historical experience has, understandably, resulted in well-founded scepticism regarding whether the single isomer should have the benefits of being considered an NAS. However, it must be recognized that there are several situations in which it would be scientifically appropriate to consider a single isomer of a racemic mixture as distinct from the racemic mixture, as follows. In all cases a single isomer would be expected to be non-equivalent clinically to the racemic mixture: 1) Both of the isomers have similar pharmacological activity but the two isomers have different safety profiles. 2) Both of the isomers have similar pharmacological activity but the two isomers have different metabolic or pharmacokinetic profiles. 3) The isomers both have pharmacological activity but the extent of this activity (on a molar basis) differs. 4) The isomers have different pharmacological activity and one of the isomers undergoes partial or complete	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		chiral conversion after administration. It must also be recognized that clinical studies demonstrating clinically significant differences the single isomer and the racemic mixture will often be infeasible, and such a requirement is contrary to the standard assumptions made in drug development. For example, two molecules that vary by a single atom that differ by, for example, 30% in half life are presumed to be clinically different. Two otherwise identical stereoisomers that present the same scenario are, undeniably, biologically different structures in the setting of the three-dimensional biological systems in which they act, and any significant differences in pharmacology or PK should be presumed to render them clinically different than the racemic mixture if any of the above scenarios apply. **Proposed change (if any):** Continue the existing paragraph, as follows: "An appropriate designation as a new active substance is critical … access to or compulsory use of the centralised procedure." "**From the scientific perspective, there are several situations to consider when assessing properties of an enantiomer with respect to differences in safety or efficacy (or both) when compared to a reference racemic mixture. In all cases the single-**	Change not accepted. The scope of the document is not to address eligibility to the centralized procedure, but the level of evidence required to confirm the designation as a new active substance. The paper allows for differences in safety or efficacy. Differences at a molar level that do not translate into clinical

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		enantiomer would be expected to be non-equivalent clinically to the racemic mixture: "**1) Both of the isomers have similar pharmacological activity but the two isomers have different safety profiles:** "**2) Both of the isomers have similar pharmacological activity but the two isomers have different metabolic or pharmacokinetic profiles;** "**3) The isomers both have pharmacological activity but the extent of this activity (on a molar basis) differs; or** "**4) The isomers have different pharmacological activity and one of the isomers undergoes partial or complete chiral conversion after administration**."	differences would not be sufficient.
Section 2 and 2.1	**3**	**<u>The test of NAS is a legal question rather than a scientific one</u>** **Comment:** The test of NAS is fundamentally a legal question, even if examination of whether it is met involves an element of scientific assessment. Indeed, it was accepted by the Rapporteur and EMA in discussions with Sunovion surrounding the assessment of Lunivia that NAS status was primarily a regulatory question and only secondarily a scientific question. It would be very unusual for a scientific advisory body to define a legal	Reference is made to Chapter 1 of Volume 2A of the Notice to Applicant where it is stated that the decision whether a different form of the active substance is to be regarded as a new active substance should be taken by the competent authorities on a case-by-case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		test, rather than simply apply it to the facts of a particular case and give guidance on the type of scientific data that it would need for assessment once the test is defined. It is only since it was determined in case law of the European Court of 2004, (later reflected in amendments to Article 6 of Directive 2001/83) that even important variants of existing products may not be treated as new products entitled to full data protection that the definition of NAS became significant in the context of data protection as well as for eligibility for the centralised system. The Court indicated that policy reasons justified restricting full data protection for the originator only to cases where the variant involved the development of NASs[2]. The concept of the Global Marketing Authorisation was developed accordingly, but the legislation did not similarly enshrine a definition of NAS beyond the indirect references to the contents of the NTA in the Annex to the Directive. If a new approach (as described in the Paper) is to be adopted in defining the meaning of NAS for the purposes of data protection, this is a matter that should first be addressed by the Commission, and as necessary the legislature. It is not appropriate that the EMA, still less	It is acknowledged that a reflection paper is not legally binding but provides clarification on the criteria to be applied in the scientific assessment of a new active substance status by the Competent Authorities.

[2] *In Novartis (Case C-106/01) the Advocate-General concluded that a policy of reserving data protection "for the most significant modifications to an original product, namely those which involve the introduction of a new active substance" was the policy that "best succeeds in balancing the conflicting objectives of data protection and the avoidance of unnecessary testing on humans and animals" (see paragraph 61). In 2004 the European Court itself followed the Advocate-General's conclusions in a decision that reflected such a policy.*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		its scientific advisory body, is asked to fill any gap in the regulatory rules, particularly where it concerns an area of law that involves a balance of sometimes conflicting public policy aims and private rights. The Paper concedes that, on the test of NAS proposed, the data requirements for licensing as safe and efficacious on the one hand, and, on the other hand, for determination of whether the differences are sufficient to designate the product as a NAS, may not be the same. We agree. Up until now the European guidance has tended to suggest that the definition of NAS is a relatively objective test concerning whether there are sufficient data from the original product to allow the proper application of the approval criteria of quality, safety and efficacy and if not, further testing was required to provide proof of the safety and efficacy of the new product. In contrast, the assessment of whether a product exhibits "clinically relevant human safety and/or efficacy differences" is essentially an exercise of comparative efficacy or safety involving determination of whether the new product represents "added clinical value". The Paper comes very close to conceding that the CHMP is embarking on an exercise of comparative evaluation that the Recitals to the Directive emphasize should not currently be part of the licensing process. Recital 34 to Regulation 726/2004 notes:	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		"Member States have developed an evaluation of the comparative efficacy of medicinal products aimed at positioning a new medicinal product with respect to those that already exist in the same therapeutic class. ... However, this evaluation should not be conducted in the context of the marketing authorisation, for which it is agreed that the fundamental criteria should be retained." If a policy based test of "added clinical value" is imposed for single isomers, what is the rationale for treating the "me too" products in a therapeutic class as NASs on the basis of their different molecular structure alone, given they are not required to demonstrate clinically meaningful differences compared to the first in class product? On any view, this is not a straightforward "technical" scientific issue. This is another reason why the EMA should carefully reflect upon whether the proposals in the Paper are consistent with the proper exercise of the EMA and CHMP powers.	It is not the purpose of the assessment of new active substance status to determine "added clinical value" but to confirm whether the enantiomer or other forms differs significantly in properties with regard to safety and/or efficacy vis-à-vis the reference active substance.
Section 2.1	**1**	**Title: Proposed change** 2.1. Criteria to be applied in deciding on whether a single enantiomer differs significantly with regard to efficacy and/or safety compared to the racemic reference medicinal product	Change proposed to address comment.
Section 2.1; 2nd bullet	**2**	**Comment:**	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		[Important] Please clarify the meaning of the term 'licensing' in this context. Does it make reference to a regulatory license (Marketing Authorisation) or does it refer to a patent license issued by a company to a third party? **Proposed change (if any):**	It makes reference to marketing authorisation.
Section 2.1; 3rd bullet	**2**	**Comment:** [Critical] It is acknowledged that a direct comparison between the racemate reference active substance and the enantiomer is a possible route to establish differences between the two. However, this is by no means the only possible route. Furthermore, in many circumstances (e.g. when an enantiomer is developed for a different indication, a different dose that is not authorised for the racemate, or differences that exist in contraindications, warnings or significant adverse drug reactions) head-to-head comparison with an unauthorised comparator would be unethical and not practically feasible. Therefore the paper should not rule out reliance on other (scientifically justified) evidence. **Proposed change (if any):** Direct comparison between the racemate reference active substance and the enantiomer is ~~required~~ one way to demonstrate the differences claimed and to justify designation as a NAS. Indirect non-comparative evidence ~~would not be suitable~~ may be acceptable if	Comment reflected in revised wording.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		scientifically justified	
Section 2.1 Criteria to be applied...	**4**	**Comment:** The last point of the section states that a direct comparison between the racemate and an investigational single enantiomer is requested. However, the "on a case-by-case basis" used later on somewhat contradicts this statement especially that examples are provided where head-to-head might not be the appropriate way.	Revised wording proposed for this section.
2.1.	**6**	We fully support the default position in the reflection paper that an enantiomer is not different from a racemate, unless proven otherwise, being in line with the approach in Annex III of Chapter 1 of the Notice to Applicants. We share the CHMP opinion that a direct comparison between racemate and enantiomer is needed to demonstrate the differences.	
2.1, line 1-3	**7**	Proposed change: Ultimately the decision on whether or not a single enantiomer is sufficiently different from an existing reference active substance will need to be made on a case-by-case basis guided by overall principles:	Change proposed to address comment.
Pg 4, Sect 2.1 (Criteria...)	**8**	**Comment:** The third bullet indicates that an enantiomer will not be considered different from a racemate unless a	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		difference is proven. Given the increased evidence and awareness of improved therapeutic profiles of single-enantiomers, as well as advances in chiral technologies, it may be prudent to adopt a more forward-looking approach that takes scientific advances into account. **Proposed change (if any):** Modify the third bullet (2.1) as follows: "For the purposes of designation as a NAS ~~only~~, the **applicant should demonstrate that the enantiomer is sufficiently different from the reference active substance.** ~~—default position is that an enantiomer is not different from the racemate, unless proven otherwise~~. For the purpose of licensing decisions, ~~there is no default position and~~ the applicant should justify its position based upon the data provided. **The basis for the separate NAS and marketing authorization decisions will be scientific assessment; there is not a default position for either decision-making process."**	Change not accepted. The default position that an enantiomer is not different from the reference active substance reflects the current legal framework, provided for in Article 10.2(b) of Directive 2001/83/EC, i.e. *'different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance unless they differ significantly in properties with regard to safety and/or efficacy.'*
Section 2.2	**1**	**Comment** We seek further confirmation regarding the interpretation that efficacy and safety must be demonstrated by head to head clinical studies. We believe that clinically relevant differences in safety and/or efficacy could be determined from purely non-	Generally one would want clinical studies – unless the differences is such that it can be accepted that the preclinical studies must lead to clinically meaningful safety or efficacy differences

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		clinical studies	
Section 2.2; last sentence	**2**	**Comment:** [Editorial] **Proposed change (if any):** In addition the package of data may include pharmacological studies, animal models of disease, and toxicological studies (if safety differences are anticipated), where these are relevant to ~~confirming~~ reflecting the clinically relevant human difference…"	Comment reflected in revised wording.
Section 2.2 Line 3	**2**	**Comment:** [Critical] 'It is therefore anticipated that head-to-head clinical studies would be required …" As indicated in our comment on 2.1, we do not agree that head-to-head clinical studies are the only way to establish a difference. **Proposed change (if any):**	Comment reflected in revised wording.
Section 2.2	**3**	**Type of evidence required to show differences** **Comment:** We see several difficulties with the Paper's proposals for the type of evidence required to classify a product as containing a NAS. • where the new product is being developed for the same indication as	This is not agreed. If it is ethically unacceptable to use the original product in the licensed indication, then the license

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		the original product, it may no longer be justified ethically to include the original product as a comparator. It may often, with the passage of time, be appropriate only to use the current standard therapy. Indeed the older product may be contra-indicated in some relevant respect. In the case of Lunivia the properties of eszopiclone supported long-term use, but zopiclone was not an appropriate comparator for long-term use as it was indicated in the EU as being for short-term use only; • where the new product is being developed for a new indication, it would be particularly problematic to start randomising patients to the original product for an indication for which it was never approved, unless there was a sound therapeutic rationale for studying the original product in that new indication; • where the new product is being developed for several indications, it is unclear how NAS classification would be determined, if the results of the comparison caused the competent authority to decide that there was "added value" for one indication, but	should not exist. There is no requirement on applicants to provide other data than that required for licensing. However, they may choose to do so in order to justify the NAS claim. If such data cannot be provided, then the default position is that the active substance is not a new active substance vis-à-vis the reference active substance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		not another. In the EU, the concept of NAS has referred to the composition of the product rather than connoting a divisible concept dependent upon indication, pharmaceutical form etc; • where classification depends upon a subjective assessment of comparative evidence of this type, it is unclear how the classification would respond to new data demonstrating a clear difference, but generated after initial approval. This might be research conducted by a different company. How is data protection to be determined where the "necessary" evidence becomes available after the new product is first authorised? Finally, the definition of NAS in the NTA focuses upon whether there are differences in properties of a single isomer that could be relevant to either safety or efficacy. In contrast, the CHMP has focused upon the results of comparative clinical trials. A head-to-head clinical trial can evaluate differences in efficacy within a statistical decision-making framework, but unless the trial programme is greatly extended, with considerable implications for cost and delay, it would tend to exclude the possibility that the difference in properties offers a benefit to meaningful sub-sets of patients. Sunovion	This situation is not affected by the development of the reflection paper. The evaluation of what constitutes a new active substance is of a scientific nature and should be performed by the CHMP or the National Competent Authority in the framework of assessment of an application for marketing authorisation. A section has been added to invite Applicants to obtain scientific advice for scenarios not covered in this reflection paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		also believes that this evidential standard has shortcomings when one is seeking to understand pharmacological differences that might impact upon safety as well as efficacy. Evaluation of safety differences are not typically made within a statistical framework based on population means. The approach of the CHMP may, therefore, undermine the aim of determining whether the different properties of the products compared may have safety implications relevant to some patients.	
2.2.	**6**	To be very precise, the NtA (annex II of Chapter I) in its definition of the New Active Substance refers to the difference in properties with regard to safety and efficacy (not safety and/or efficacy).	Reference is made to Article 10.2(b) of Directive 2001/83/EC, i.e. *'different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance unless they differ significantly in properties with regard to safety and/or efficacy.'*
Pg 4, Sect 2.2 (Type of evidence...)	**8**	**Comment:** There may be certain instances when other data sources could be helpful. For example, pharmacoepidemiologic data could be helpful to better characterise safety and effectiveness data of the reference active substance. Microbiologic data could be helpful in assessing anti-infectives. **Proposed change (if any):** Modify the paragraph as follows: "In addition the package of data may include	"or other data" has been added which allows for pharmacoepidemiologic data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		pharmacologic~~al~~ **or pharmacoepidemiologic** studies, animal models of disease, **microbiologic studies**, and toxicological studies (if safety differences are anticipated), where these are relevant to confirming the clinically relevant human difference, or have been conducted…"	
Section 2.3	**1**	**Proposed change: Title** What might constitute a significant difference in safety and/or efficacy to justify that ~~a product is~~ an enantiomer is a new active substance?	Change done to reflect the final scope of the reflection paper.
Section 2.3	**1**	**Comment:** We agree with the bullet points as to what might be regarded as sufficiently significant difference, however we suggest these could be established without head to head clinical trials if the scope of this paper is for reference medicinal product and includes enantiomeric active substances that are subject to complete development, and do not rely on previous findings of safety and efficacy of a reference medicinal product	Consideration of an active substance as new active substance is not dependent on whether it was subject to a complete development or not, but on whether the enantiomer or other forms differs significantly in properties with regard to safety and/or efficacy vis-à-vis the reference active substance.
Section 2.3; first sentence	**2**	**Comment:** [Editorial] Suggestion to emphasize that each of the points mentioned is sufficient to demonstrate a significant difference. **Proposed change (if any):** "Whilst this would need to be considered on a case-by-	Change proposed to address comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		case basis, it is anticipated that one of the following might be regarded as sufficiently significant differences."	
Section 2.3 Bullet points	**2**	**Comment:** [Important] With reference to our previous comments, the following are examples of differences that can be addressed without directly comparative trials and/or would be impractical or unfeasible to address in directly comparative trials: • Significant changes in dosing frequency • Meaningful and clinically relevant changes that affect drug: drug interactions • Direct comparison to demonstrate clinically significant differences in contraindications or the possibility to use the drug in a previously excluded sub-group would necessitate the approved racemate to be tested in situations that are contraindicated. **Proposed change (if any):**	The wording of 2. has been modified to acknowledge the possibility to demonstrate significant differences in safety and/or efficacy without directly comparative trials.
Section 2.3 What might constitute...	**4**	**Comment:** From the first bullet point, significant changes in dosing frequency (e.g. bid to od), which is only a pharmacokinetic parameter, could indeed provide a significant benefit to patients and does not warrant necessarily head-to-head studies. This illustrates some inconsistency in the draft reflection paper.	The wording of 2. has been modified to acknowledge the possibility to demonstrate significant differences in safety and/or efficacy without directly comparative trials.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Furthermore, the end of the sentence: "…if this is deemed to be clinically significant" leaves a great deal of uncertainty in relation to this situation.	
Section 2.3 What might constitute...	**4**	**Comment:** The issue of clinically relevant difference in the primary endpoint (in the second bullet point) is still unclear. It should be defined/justified or otherwise open to debate. The same goes for clinically significant differences in contraindication, adverse reactions (in the third bullet). These two issues leave an important amount of uncertainty and are often left to judgement.	
Section 2.3 What might constitute...	**4**	**Comment:** Bullet points four and five are relevant, but it is not clear how such differences can be tested. Indeed, a difference that may enable more patients or previously excluded subgroups to take the drug is a potentially significant benefit to patients. However, in practice, that would be a very difficult aim to target given that the drug will have to be tested specifically in contraindications, which would raise ethical issues. Moreover, such investigation would not need head-to head trials, which illustrates further the lack of	A comment has been added regarding demonstration of differences in interaction studies. Provision is now made for compelling data other than head to head data to be allowable.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		consistency in the draft reflection paper. **Proposed change:** It is proposed that the principle of requiring head-to-head trials to demonstrate difference of an enantiomer should be deleted given that many examples go against this reasoning and that this would set a too high – and in some instances, inappropriate – standard to leave room for innovation.	
Paragraph 2.3, first bullet-point	**5**	**Comment:** This example may be misleading in a sense that a change in dosing frequency will not be clinically significant if the safety and efficacy of treatment remains unchanged. It is therefore proposed to omit this example or to rephrase it, making it more clear that the change in posology should be a result of a significant change in safety of efficacy. **Proposed change (if any):** • Significant changes to the dosing frequency (e.g. bd to od) mandated by ~~the~~ clinically significant differen~~t~~ces ~~properties~~ in safety or efficacy of the enantiomer~~, if this is deemed to be clinically significant~~; However, preferred to be fully deleted.	Change accepted.
Paragraph 2.3,	**5**	**Comment:** We agree that preclinical data alone (without clinical	Change not accepted, as differences in reproductive toxicity or

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
second bullet-point of 'Evidence unlikely to be sufficient'		confirmation) are in general not sufficient to show a difference. However, it is suggested not to list the examples of possible exceptions since, also in these cases, there will be discussion on the clinical relevance. **Proposed change (if any):** • Preclinical differences without clinical confirmation ~~(with the possible exception of differences in reproductive toxicity or carcinogenicity)~~;	carcinogenicity may not be possible to be confirmed in a clinical setting.
2.3, 1st bullet point Significant change to the dosing frequency	**6**	The change of the dosing frequency within the same pharmaceutical form (e.g. from twice daily to once daily) is positive for patient compliance but should not be considered sufficient to support a classification as NAS. In case of comparative studies, the adjustment of the dose between racemate and single enantiomer should be taken into consideration. As the enantiomer is expected to have a higher activity than the racemate, there might be some confusion in interpretation. **Proposed change (if any):**	
2.3 2nd bullet point Meaningful changes to	**6**	The EGA supports the necessity to prove the meaningful changes to the overall efficacy by showing clinically and statistically significant difference in the primary endpoint.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
the over efficacy		In line with the comments above, the dose adjustment between racemate and single enantiomer should be taken into consideration when the conclusion is made. The clinical studies should be performed with an effective dose of single enantiomer versus an effective dose of racemat, even if doses are different. **Proposed change (if any):**	
2.3 3rd and 4th bullet points Different populations	**6**	We support the status of NAS if the substance can be used in a population previously excluded based on the outcome of studies on racemate. The widening of the population for single enantiomer in the case where the racemate has not been tested on this population, should not be considered as sufficient argument to grant the status of NAS. If the paediatric population is concerned, the obligation related to the Paediatric Regulation should be fulfilled first to assess whether the product is appropriated for this population. **Proposed change (if any):**	Change proposed to address comment.
Pg 4, Sect 2.3 (What might ...)	**8**	**Comment:** Significant differences in efficacy or safety, e.g., for anti-infective or anti-cancer agents, may be assessed via surrogate markers. Likewise, the evolving role of pharmacogenetic markers, with appropriate specificity, should be recognised.	Change proposed to address comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Add a 6th bullet to the list (top pg 5, following "Meaningful … in a wider patient population or previously excluded sub-groups."): • **"Consistent with the progress of medical science, differences in safety and/or efficacy or use in special populations may be supported using surrogate markers or sufficiently specific pharmacogenetic markers, etc."**	Change not considered necessary, as the same standards apply in relation to the choice of endpoints for clinical trials for licensing.
Section 2.4	**1**	**Comment:** The assessment of designation by the CMDh for non-centralised procedures does not appear appropriate for purely national submissions. The CMDh is empowered for "the examination of any question relating to marketing authorisation of a medicinal product in two or more Member States in accordance with the mutual recognition procedure or the decentralised procedure." **Proposed change (if any):** It is therefore proposed that such designations are agreed at either the Committee for Medicinal Products for Human Use (CHMP) (for products handled via the centralised procedure) or the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh) (for products handled through ~~national,~~ mutual recognition or decentralised procedures) and the NCAs for national procedures.	This section has been removed from the reflection paper as it deals with regulatory aspects, which are not covered by this reflection paper.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Section 2.4	**2**	**Comment:** [Critical] "It is important that the status of a medicinal product is appropriately determined at the time of first approval…." We are concerned about the proposed timing for designation. In order to include such considerations into industry decisions on development programmes, this information would be required considerably earlier. We would welcome a dialogue, e.g. in the form of scientific or regulatory advice that provides sufficient certainty to industry on the outcome of the designation. (see also comment on Section 3) **Proposed change (if any):**	Scientific advice is an option, but final determination will only happen at the time of review of the marketing authorisation application. This section has been removed from the reflection paper as it deals with regulatory aspects, which are not covered by this reflection paper.
Section 2.4	**2**	**Comment:** [Critical] The guidance is not clear on the practical details of how the designation of NAS would be achieved. It should e.g. be clarified if the actual designation would be at the MS level, and if it would be binding on the MS. The right for the sponsor to appeal a decision, to whom the appeal should be made and the associated procedure should also be specified. **Proposed change (if any):**	This section has been removed from the reflection paper as it deals with regulatory aspects, which are not covered by this reflection paper.
Paragraph 2.4	**5**	**Comment:** We fully agree that a discussion should be carried out at	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		a European level. However, for national, MRP and DCP products there is no formal mandate for CMD (only in case of a referral CMD would formally be involved). To avoid any discussion on accurate decision making it is proposed to amend the text as indicated below. **Proposed change (if any):** It is critical that decisions taken on designation of a substance as a NAS compared to an existing reference active substance are robust and agreed at a European level. It is important that the status of a medicinal product is appropriately determined at the time of first approval, and explicitly concluded in the published Assessment Report. ~~It is therefore proposed that such decisions are agreed at either~~ <u>For products handled via the centralised procedure such decision will be agreed by</u> the Committee for Medicinal Products for Human Use (CHMP) ~~(for products handled via the centralised procedure) or~~ <u>For products handled through national, mutual recognition or decentralised procedures it is highly recommended to agree such decision by</u> the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMD(h)) ~~(for products handled through national, mutual recognition or decentralised procedures)~~.	This section has been removed from the reflection paper as it deals with regulatory aspects, which are not covered by this reflection paper.
2.4 Ensuring robust	**6**	We fully support the statement that designation of a substance such as a NAS compared to an existing reference active substance, should be robust and	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
designations		agreed at a European level. The consistency in the decision making process, independently of the MA procedure chosen, is essential. We also fully support the importance of determining the status of a medicinal product at the time of first approval, and explicitly concluded in the published Assessment Report. It brings clarity regarding possible filing of a generic application and when the generic competition can start.	
2.4 line 1-2	**7**	Proposed changes: It is critical that designation …. is unequivocal…	This section has been removed from the reflection paper as it deals with regulatory aspects, which are not covered by this reflection paper.
Section 2.5 Title of the section	**2**	**Comment:** [Editorial] This section refers to "filing route" and "legal basis" of a marketing authorisation. This should be reflected in the section title. **Proposed change (if any):** "Significance of filing route or legal basis of marketing authorisations"	Change accepted.
Section 2.5 Last sentence	**2**	**Comment:** [Important] With reference to the data exclusivity obtained when the NAS status for the enantiomer is confirmed, it is recommended to specify that an Article 10(1) generic application or 10(3) hybrid application for the enantiomer may only refer to the enantiomer as reference product, while such an application for the racemate may only refer to the racemate as reference	Regulatory consequences of designation as new active substance have been removed from the reflection paper, as these stem from the legislation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		product. The data exclusivity period for each reference product should be duly respected before validating such an application. **Proposed change (if any):**	
Section 2.5	**3**	**<u>Significance of filing route</u>** **Comment:** The Paper concedes that the application of test of the NAS put forward "can only be made after a detailed assessment of the application". There is considerable tension between such an assessment and the historical approach to eligibility for centralised assessment based upon being a NAS. A preliminary assessment of the properties of a product in terms of pharmacokinetics and pharmaco-dynamics can readily allow a conclusion that data relating to the original product are insufficient and the new product must be treated as a NAS for regulatory assessment purposes, and is eligible for centralised assessment. In contrast, if eligibility for centralised assessment requires the completion of the assessment process (as occurred in relation to Lunivia) and the product is then deemed not to be a NAS, it necessarily follows that it was never eligible for centralised assessment in the first place. The Commission has no power to issue an authorisation under the Regulation and the fees should be returned to the applicant. The previously well-established pre-	

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		application procedure to judge eligibility that envisaged eligibility to be finally determined no later than validation of the application becomes unworkable. In the case of Lunivia, part way through assessment the EMA suggested that there existed a two stage test that involved an "access test" of NAS based upon Annex III to the NTA (which we had passed) and a "licensing test" requiring the applicant to prove meaningful clinical differences (which the EMA determined we had failed under the newly proposed head-to-head, controlled clinical trial standard, although it should be noted that Sunovion vehemently disagrees with that assessment based upon the evidence submitted). Neither the origin nor basis for this two stage test was ever explained and it should now be explained in the Paper. No other guidance on the operation of the centralised system describes such an approach to eligibility.	It has been clarified in the reflection paper that the outcome of the assessment on whether an active substance is to be considered as a new active substance has no impact on previously granted access to the centralised procedure.
2.5. Significance of filing route	**6**	The EGA fully endorses the statement that filing under Article 8(3)(i) of Directive 2001/83, as amended, does not automatically confer a NAS status, nor does filing through the centralised route. Indeed, a decision on designation as a NAS can only be made after a detailed assessment of the application by the competent authorities, not by choice made by the applicant.	
Section 3	**2**	**Comment:** Consideration should be given to a different assessment	

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		process, i.e. the Rapporteur or RMS or Competent Authority should agree on NAS status. In this way, review of the MAA culminating in a negative outcome due to NAS designation can be avoided. **Proposed change (if any):**	
3. Conclusions	**6**	We very much appreciate the intention to bring clarity in the decision making process for new applications. The generic medicines producers are facing uncertainty regarding the Marketing authorisations granted in the past where clear judgement was not made nor communicated by the Competent Authorities in publically available Assessment Reports. Some clarification will be welcomed on how to apply the above presented criteria to already granted MAs and whether the same scientific approach can be extended to other cases of possible differences, not only to enantiomer/ racemate. The clear conclusion and justification as to whether the substance is considered as a new (NAS) or not, should routinely be a part of the EPAP/ PAR published by the Competent authorities at the end of the MA process.	The scope of the reflection paper has been extended to include the other forms referred to in Article 10.2(b) of Directive 2001/83/EC. There is no retroactive effect of the reflection paper on previous NAS designations of single enantiomers. The evaluation of what constitutes a new active substance is of a scientific nature and should be performed by the CHMP or the National Competent Authority in the framework of assessment of an application for marketing authorisation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
3. Conclusion	**7**	Comment: It is not clear what is meant by "newly assessed" and the suggested process is not clearly described. Proposed changes (if correctly understood): ….should recommend whether or not the enantiomer is to be considered as a NAS in relation to the relevant racemic reference substance and seek agreement within CHMP/CMdH prior to concluding the matter. The assessment proposal will be published in the Assessment Report and has to be followed for future generic/hybrid applications.	Revised wording proposed for this section.
Section 4 References	**2**	**Comment:** Please include a reference to the 'Chirality Guideline' **Proposed change (if any):** Please add: "- Guideline Investigation of Chiral Active Substances 3CC29a"	Change not accepted.