EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Submission of comments on 'Reflection paper on criteria to be considered for the evaluation of new active substance (NAS) status of biological substances' (EMA/CHMP/CMDh/CAT/BWP/828612/2022)

Comments from: EFPIA

Name of organisation or individual
EFPIA

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	There are some concerns that EMA may be performing a more stringent assessment of Applicants' justification for NAS status and it is unclear what motivated the change in approach to assessment of NAS eligibility at EMA. - More extensive comparisons are being requested and Applicants are requested to provide all of the results of searches and comparisons performed. Applicants are now being asked to prove a negative. - If the current trend continues then it may become more difficult to obtain NAS status if EMA is applying a higher standard for grant of NAS status, with the consequence being that the regulatory and IP implications will likely be realised more often. - **EFPIA would welcome the opportunity to engage with EMA experts in a workshop to further discuss the proposals outlined in this draft Reflection Paper.**	
	<u>Purpose of NAS assessment</u> According to EMA's presentation in 'New Active Substance categorisation and Orphan Similarity' (https://www.ema.europa.eu/en/documents/presentation/presentation-new-active-substance-categorisation-orphan-similarity-piotr-kozarewicz_en.pdf), the spirit of the legislation concerning assessment of eligibility for NAS status is to "*encourage innovation whilst preventing from gaining rewards on the back of another's efforts*". It is respectfully submitted that this is not the lens through which justification of eligibility of	

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	NAS status should be examined. It will result in an assessment of eligibility for NAS status that is subjective rather than objective assessment, which appears to be manifesting itself in this draft reflection paper. More specifically, if the 'basic structural element' of a biological substance differs from the 'basic structural element' of an already approved biological substance such that it cannot rely on the data package of the already approved biological substance as a reference product for a MAA in accordance with Article 10 of Directive 2001/83/EC, then an objective assessment of NAS should reach the conclusion that the biological substance is new. Such a biological substance does not gain a '*reward on the back of another's efforts*' because a full data package is required for that biological substance to be approved in accordance with Article 8(3) of Directive 2001/83/EC. Assessing instead, whether a modification to a "basic structural element" is "substantial" as proposed in the reflection paper under the first indent for biological substances invites subjective assessments of whether an indisputably novel/new active substance is sufficiently different from a previously approved active substance.	
	<u>Importance of regulatory consistency for the criteria under indent 1</u> For the NAS assessment under indent 1, the draft reflection paper only focuses (for products other than ATMPs) on the therapeutic moiety of the product and defines that as the "basic structural element(s)" or "core structure", at the exclusion of "added functional molecular structures" (lines 148-155 and 476-477).	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	There is a fundamental problem with this criteria – there is no definition of 'therapeutic moiety' anywhere in the legislation or relevant guidelines. Therefore, if it is not possible to objectively determine what is the 'therapeutic moiety' in a medicinal product, then it is not possible to objectively determine whether a chemical or biological active substance is the same therapeutic moiety. The assessment of eligibility for NAS can become a subjective one. This manifests itself in the present draft reflection paper with an EMA examiner / Rapporteur making a determination about whether or not a change to the 'basic structural element' of a biological substance is substantial enough to just eligibility for NAS under the first indent. Additionally; the new reflection paper must fit within the broader context of EU rules and guidelines governing biological medicinal products and be consistent with the regulatory approach to such medicinal products. This is, in particular, relevant for the assessment of structural differences between related biological active substances. For the NAS assessment under indent 1, the draft reflection paper only focuses (for products other than ATMPs) on the therapeutic moiety of the product and defines that as the "basic structural element(s)" or "core structure", at the exclusion of "added functional molecular structures" (lines 148-155 and 476-477). This approach is, however, not consistent with the principles of similarity under the orphan medicinal products rules and the rules on variations to marketing authorisations: • Detailed rules on how to assess similarity of	

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	biological active substances are laid down in Commission Regulation 847/2000 (as amended in 2018). This is based on the concept of principal molecular features. Article 3(3)(c)(2) provides that for biological active substances (other than those of ATMPs): *"The principal molecular structural features are the structural components of an active substance that are relevant for the functional characteristics of that substance. The principal molecular structural features may be composed of a therapeutic moiety or a therapeutic moiety in combination with an additional structural element(s) significantly contributing to the functional characteristics of the active substance.* *Such an additional structural element(s) can be conjugated, fused or linked by other means to the therapeutic moiety or can be an extension of the therapeutic moiety protein backbone by additional amino acids. Substances with structural elements for which similar methods of modification or conjugation technology are used shall normally result in similar substances."* It is very clear that the concept of similarity (under the orphan medicines rules) is thus not limited to the therapeutic moiety of the molecule, but can also include other structural	

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	elements when they make a significant contribution to the functional characteristics of the active substance. For proteins, this means that some post-translational or chemical modifications (e.g., different glycosylation patterns) may result in a determination of non-similarity provided that there is significant effect on the functional characteristics of the substance. The draft reflection paper, however, proposes to ignore the same post-translational or chemical modifications for a NAS determination under indent 1. This is not consistent because the orphan medicines principles on similarity are also based on the molecular structure of the active substance (while the concepts of clinical superiority and of NAS status under indent 3 are mainly based on the safety and efficacy profile of the product). In addition, when an active substance, based on the molecular structure, is not "similar" under the orphan medicines rules, it can logically also not be the "same" for purposes of a NAS assessment. On that basis, the reflection paper should also allow for a NAS determination under indent 1 based on other structural elements when they make a significant contribution to the functional characteristics of the active substance. Demonstration of the significant contribution to the functional characteristics of the active substance should be based on scientific literature, *in vitro* or *in-vivo* non-clinical data.	

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	• The same approach is reflected in the Commission Regulation 1234/2008 on variations. Annex I defines what changes can qualify as a marketing authorisation extension. It includes the *"replacement of a biological active substance with one of a slightly different molecular structure where the efficacy and/or safety characteristics are not significantly different, …"* This is thus clearly not limited to the "basic structural element(s)" or "core structure of the active substance" (as suggested in the draft reflection paper), but instead requires an assessment of the molecular structure as a whole. That structure can at most show "slight" differences with the pre-existing molecular structure to qualify as an extension. By analogy all elements of the molecular structure can be relevant for the NAS assessment under indent 1. Further confirmation of these points is provided in the general EMA Guideline on similar biological medicinal products (CHMP/437/04 Rev 1). The guideline provides that "intended changes to improve efficacy (e.g. glyco-optimisation) are not compatible with the biosimilarity approach" (page 5). This demonstrates the relevance of functional structures, while the draft reflection paper excludes functional molecular structures from the concept of a basic structural element. It is also logical that when a specific aspect of the molecular structure excludes an active substance from qualifying as a biosimilar, it has to qualify as a NAS under indent 1.	

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	Based on these elements, the reflection paper on the NAS status of biological active substances should recognise the relevance under indent 1 of all molecular elements that influence the functional characteristics of the active substance. This can be done in two ways: either by specifically mentioning that other molecular elements than the therapeutic moiety are relevant; or by defining the therapeutic moiety as including these other elements. Finally, the NAS status forms part of the general regime of data and marketing protection for new medicines. This is clear from the reference to Annex I to the Notice to Applicants (in lines 80 and following) and the link in the Notice to Applicants between Annex I and the global marketing authorisation concept. In order to preserve the function of the data and marketing protection system as an incentive, it must be possible to support a NAS finding under indent 1 also based on the functional characteristics of elements that are linked to the core structure of a biological active substance, and to demonstrate these characteristics also on the basis of scientific literature, *in vitro* or *in-vivo* non-clinical data. Indeed, pre-clinical data should be sufficient to demonstrate that the changes to a molecule render it significantly different to a previously approved drug to justify NAS status. Such pre-clinical data is typically used to convince regulators that the medicinal product warrants clinical investigation. The same data may also be used to justify the inventiveness and thus patentability of the molecule at the European Patent Office. If pre-clinical data demonstrates that changes to the basic structural element make a significant contribution to the functional characteristics of the active substance, then this should be sufficient to justify	

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	NAS status under indent 1.	
	Ambiguity around whether a new drug approved without NAS status is a biosimilar – or neither a NAS nor a biosimilar The draft reflection paper makes clear that if changes to the amino acid sequence of a biologic relative to an earlier approved biologic are not considered substantial, then that biologic is considered to be the same medicinal product as the earlier approved biologic. It is unclear whether such a biologic would be considered to be a 'similar biological medicinal product' (i.e. biosimilar) in accordance with Article 10(4) of Directive 2001/83/EC. This ambiguity arises because Section 5.3.1 of the 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance:[1] quality issues' states that "*[t]he target amino acid sequence of the biosimilar should be confirmed and is expected to be the same as for the reference medicinal product*". In other words, eligibility for bridging to a Reference Product's data package under EMA guidelines is appropriately conditioned on require a biosimilar having the same amino acid sequence as the reference medicinal	

[1] 22 May 2014 EMA/CHMP/BWP/247713/2012 Committee for Medicinal Products for Human Use (CHMP). The same point about inconsistencies between Regulations can be highlighted referring to the Regulation 1234/2008 on variations. Annex I defines what changes can qualify as a marketing authorisation extension. It includes the "*replacement of a biological active substance with one of a slightly different molecular structure where the efficacy and/or safety characteristics are not significantly different, …*" This is thus clearly not limited to the "*basic structural element(s)*" or "*core structure of the active substance*" (as suggested in the draft reflection paper), but instead requires an assessment of the molecular structure as a whole. That structure can at most show "slight" differences with the pre-existing molecular structure to qualify as an extension. By analogy all elements of the molecular structure can be relevant for the NAS assessment under Indent 1.

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	product. In contrast, these passages (lines 155-167 and 384-406) introduce the possibility that a novel biologic, i.e., one that does NOT have the same primary amino acid sequence of its reference product, will not be a NAS and would not be a biosimilar either. The consequences of this ambiguity are: • *lack of definition of the therapeutic moiety and of substantial difference introduces subjectivity into the assessment of eligibility for NAS under indent 1.* • *Unclear what standard will be applied by EMA when assessing whether changes are substantial* The draft reflection paper proposes that for proteins, "showing substantial differences in the amino acid sequence constituting the basic structural element" would likely be enough to be considered NAS (lines 159-161). However, the paper does not provide any criteria for determining such "substantial" differences. If the assessment will involve some degree of subjectivity, it is not clear what standard will be applied when determining whether change(s) to the "basic structural element" are substantial. In the absence of detailed guidance, the determination of whether change(s) are substantial is highly subjective and will likely lead to different outcomes despite similar facts	

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	and circumstances. There are two ways to resolve this ambiguity: 1/ objective assessment of either a biological substance is new, i.e. any difference in the molecular structure, including post-translational modifications, justifies eligibility for the NAS status under indent 1. or 2/ analysis of the impact of any molecular differences, including post-translational modifications, on the functionality. i.e. that differences in amino acid sequence and / or post translational modifications should be considered "substantial" for eligibility to NAS status under indent 1 if they are linked to the functional characteristics of the protein and not to the number of different amino acid residues.	
	<u>Notion of substantial difference in AA sequence:</u> The draft reflection paper proposes that for proteins, "showing substantial differences in the amino acid sequence constituting the basic structural element" would likely be enough to be considered NAS (lines 159-161). However, the paper does not provide any criteria for determining such "substantial" differences. Differences in amino acid sequence should be considered "substantial" if they are linked to the functional characteristics of the protein and not to the	

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	number of different amino acid residues. Consequently, any difference in amino acid sequence impacting the protein's functionality, supported by scientific literature, in vitro or in-vivo non-clinical data, should be sufficient to claim a NAS status under indent 1.	
	Level of evidence for indent 3: The draft reflection paper proposes a flexible standard of "plausible scientific grounds" for demonstrating significant differences in safety or efficacy properties for ATMPs under indent 3. This reflects the specific nature of the products. Similar considerations apply, however, also to other biological medicines, and in particular to those that have similar structural characteristics to ATMPs or that are intended for patients that suffer from rare diseases. The standard under indent 3 should also allow for plausible scientific grounds for these products because at the time of the initial marketing authorisation only limited clinical data may be available and thus not allow for clear evidence of a significant difference in safety and/or efficacy properties. Therefore, for such medicinal products a justification based on "plausible scientific grounds" supported by scientific literature and/or available data (not necessary clinical data, in particular a head-to-head trial demonstrating statistical clinical superiority) should be accepted.	
	Importance of early-stage clarity on methodologies substantiating NAS claim to improve predictability of NAS status:	

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	NAS status crucially drives data and marketing protection, and may also impact supplementary protection certificate and pricing and reimbursement, and hence even patient access to innovative new medicines. Applicants invest considerable time and resources in designing and performing the studies and associated work necessary to apply for marketing authorisation . It is respectfully submitted that, in the absence of objective NAS criteria (for which we advocate), the determination of NAS status occurs too late in the regulatory approval process. For instance, for justification of NAS under the third indent, head-to-head studies demonstrating improvements in terms of efficacy and / or safety may be required in certain circumstances. The assessment of NAS, however, is performed AFTER the clinical studies on the medicinal product have been completed. Very often, the clinical trials of a medicinal product have been designed without head-to-head studies. This could leave Applicants for a marketing authorisation in the unenviable position of being refused NAS under the first indent but without the data to justify NAS under the third indent because the required studies were not performed. It is therefore of great importance to applicants to have the possibility to obtain already in the early development phase of a new medicine clarity as to whether the methodologies they are considering for substantiating a NAS claim will be accepted by the CHMP at the time of conducting the NAS assessment as part of the MA procedure. In this context, it is welcomed that the new reflection paper encourages applicants to obtain scientific advice from the CHMP on NAS related matters, with the expectation that this will also enable	

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	applicants to obtain scientific advice with clear and comprehensive CHMP conclusions on the (non-) acceptance of proposed methodologies for substantiating a NAS claim.	
	The breadth and complexity of the biological products in scope of this guidance mean that an exhaustive, overly technical guidance is not be preferred as it would require rapid revisions to align with novel innovation and emerging science. However, there are some areas where additional non-exhaustive examples are requested to provide clarity for existing biological substances. **mRNA-based molecules:** Does not appear to have clear guidance on the NAS considerations for mRNA or nucleic acid-based active substances. Given that there are some key differences between substances derived by recombinant vs ATMP, it is hard to understand which group mRNA-based molecules seem to be anchored. **Novel vaccines:** (section 5.Q&A) for new active biological substance, pg. 13 - The reflection paper could benefit from the addition of a separate subsection to provide requirements for active substances which may be live attenuated viral vaccines or mRNA vaccines, which are not classed as ATMPs. These are only very briefly mentioned in "5.Q & A for new active biological substance, examples 4 and 8", and are not covered in sections 3.1 or 4.1 **Combined ATMPs:** (section 4.1.1) Cell-based and tissue engineered products - The reflection paper could benefit from addition of non-exhaustive examples on	

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	requirements for combined ATMPs (e.g. cells seeded onto or into a biodegradable scaffold/medical device, with the cell seeded scaffold being considered the active substance). These are not covered. For instance, readers of the guidance may what to understand whether changes to the scaffold could constitute a new active biological substance. **ATMP Constructs:** (Section 4.1 Line 254) Comment: The reflection paper could benefit from addition of non-exhaustive examples to illustrate that NAS status is possible when a cell or gene therapy may have a similar or identical construct with the exception of the gene of interest. That is not clear in the document. **Variants and additional structures:** (Lines 170-172) The reference to "additional structures or a change in relative proportion of the various structures" is unclear. We suggest proposing examples or clarification of new and relative proportion of variants that might lead to designation as NAS, without making such examples exhaustive. **Combination of active substances:** (Lines 182-191) The focus of the paragraph is unclear. The terminology "combination of active substances" could be applied to antibody-drug conjugates or combination therapies. Is this paragraph referring to combination therapies as well as antibody-drug conjugates? Please clarify if combination therapies (along with antibody-drug conjugates) are the subject of the paragraph on lines 182-190. Please provide an example for combination therapies (with two distinct active substances) if they are to be included in this paragraph	

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	Different manufacturers or different manufacturing process Lines 447-457: It is unclear what criteria would be utilized to justify a new active substance based on the use of different manufacturers or different manufacturing process. Can the response to Question #6 specify criteria to consider for NAS when different manufacturer or different process are used without making such examples exhaustive or refer back to a section within the guidance that covers that detail.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using "track changes")*	Outcome *(To be completed by the Agency)*
100-102		Comment: We propose that the following additional text should be added to the guideline to clarify where comparative data to similar products should be included in the dossier: Proposed change: ***Module 3.2.S should contain only the data on the NAS being claimed. For a new active substance claim for a biological substance not previously authorised in a medicinal product for human use in the European Union, but for which the applicant needs to provide explanation about how the active substance differs from a previously approved biological substance [see section 3.1 of the reflection paper] the corresponding justification should be provided as Annex 5.23 to the Application Form. For a new active substance claim for a biological substance previously authorised but differing significantly in properties with regard to safety and/or efficacy, which is due to differences in one or a combination of molecular structure, nature of the source material or manufacturing process, information on the claimed differences [see section 3.2 of the reflection paper] i.e. the corresponding justification, should be provided as Annex 5.23 to the Application Form.***	
113-115		Comment: The document does not provide guidance regarding what the 'basic structural elements' are to be compared against. Applicants have noted that different approaches are being applied by EMA when assessing eligibility for new active substance. For example, in respect of antibodies, Applicants have in certain instances been requested to compare a 'new' antibody that binds to a certain target against other antibodies that bind to the same target. In other instances, however, Applicants have been requested to compare a 'new' antibody that binds to a certain target against ALL approved antibodies, irrespective of the target to which the approved antibody binds. Given the	

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		specificity of an antibody resides in its variable regions, the former approach rather than the latter appears to be justified from a scientific perspective and any difference in amino acid residues in these regions should objectively lead to a NAS determination. Nevertheless, guidance that encourages a consistent approach to assessment of NAS status is recommended in order to provide certainty to Applicants. Proposed change: (i) Line 115, after "*…(see Glossary)*: **with the basic structural element of already approved active substances in the same structural and functional class (see Glossary). For instance, the basic structural element of a protein (primary amino acid sequence) should be compared with the basic structural element of other approved proteins that bind to or interact with the same target."** (ii) New definition of "structural and functional drug class" to be included in the Glossary on pages 13-15: **"Structural and functional drug class** **Broad classification of drugs according to their structure (e.g. small molecule, antibody, peptide, siRNA etc.) and their mechanism of action. For example, antibodies that bind to target X are in the same structural and functional class and a new antibody to target X must be compared against other approved antibodies that bind to target X. It is not necessary to compare the antibody that binds to target X against antibodies that bind to target Y."**	
130-131		Comment: It is unclear what amino acid sequence is referenced to. Proposed change: "amino acid sequence **of a new active protein or peptide**"	
148-155		Comment: As mentioned in the general comments "Importance of regulatory consistency for the criteria under indent 1" and "Ambiguity around whether a new drug approved without NAS status is a biosimilar", the proposal to use the	

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		therapeutic moiety for the assessment of eligibility for NAS under the first indent is inconsistent the broader context of EU rules and guidelines. It is also inconsistent with the concept of comparability for well characterised biologics. If a change to the basic structural element is not considered substantial and therefore does not justify eligibility for NAS status, then there is a tension with current concepts on comparability of biological products (see, for example, https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-5-e-comparability-biotechnological/biological-products-step-5_en.pdf). EU guidance on the concept of "Alternate Processes" (best described in Section 6.3 of Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission ""EMA/CHMP/BWP/187338/2014); https://www.ema.europa.eu/en/process-validation-manufacture-biotechnology-derived-active-substances-data-be-provided-regulatory) makes clear that even if comparability is demonstrated, there is sufficient concern that divergent process changes at different sites may cause product quality (especially PTMs) to diverge such that the divergent processes are considered to be alternate processes with such alternate processes requiring assessment and approval by the regulator. The concepts presented here and guidance on "alternate processes" should not be mutually exclusive. According to Section 2 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*", a chemical active substance that is not previously authorised in a medicinal product for human use in the European Union and that is, from a chemical structure point of view, not related to any other authorised substances should be considered as a NAS. 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. According to the guidance in that reflection paper, any structural change to an already approved small molecule's active moiety (e.g. a seemingly "small" change like one different substituent on a benzene ring, or one different amino acid in a peptide mimetic) is sufficient to justify a NAS designation provided the patients are	

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		exposed to a different therapeutic moiety. This is sensible when one considers that the modified small molecule or peptide must be supported by a full data package to obtain marketing approval from EMA or national medicines agencies in Europe and where any such structural differences are expected a priori to result in a different safety/efficacy profile among the molecules. Moreover, it is not permissible to rely on the data package of a reference product if it is structurally different from the reference product. To be consistent with other regulatory guidance, the reflection paper should also allow for a NAS determination under indent 1 based on other structural elements when they make a significant contribution to the functional characteristics of the active substance. Demonstration of the significant contribution to the functional characteristics of the active substance should be based on scientific literature, in vitro or in-vivo non-clinical data. Proposed change: "Such substance is considered to be new in itself provided that the administration of the applied active substance would not expose patients to the same therapeutic moiety as already authorised active substance(s) in a medicinal product in the European Union. **Additionally, a difference in other molecular elements that significantly impact the functional characteristics of the active substance, as demonstrated by scientific literature, in vitro or in-vivo non-clinical data could also support a NAS claim under indent 1.**"	
155 – 167		Comment: As mentioned in the general comments "Importance of regulatory consistency for the criteria under indent 1", "Notion of substantial difference in AA sequence" and "Ambiguity around whether a new drug approved without NAS status is a biosimilar", this proposal clearly introduces subjectivity into the assessment of eligibility for NAS under the first indent as it is not clear what standards will be applied when determining whether a change is "substantial".	

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		For example, consider the possible divergence between assessment of NAS for a synthetic incretin mimetic and assessment of NAS for a recombinant incretin mimetic, both of which have the same primary amino acid sequence. The synthetic incretin mimetic for which approval and NAS status is being sought has two amino acid changes relative to an already approved synthetic incretin mimetic. This synthetic incretin mimetic obtains NAS status under the first indent because the therapeutic moiety that the patient receives is different from the already approved synthetic incretin mimetic. The biologic incretin mimetic for which approval and NAS status is being sought has two amino acid changes relative to an already approved biologic incretin mimetic. In the absence of objective criteria, the biologic incretin mimetic may not qualify for NAS status under the first indent if the amino acid changes are not considered "substantial". Differences in amino acid sequence should be considered "substantial" if they are linked to the functional characteristics of the protein and not to the number of different amino acid residues. Consequently, any difference in amino acid sequence impacting the protein's functionality, supported by scientific literature, in vitro or in-vivo non-clinical data, should be sufficient to claim a NAS status under indent 1. Proposed change: "Importantly, changes introduced in the basic structural element should be substantial to warrant a conclusion of NAS (e.g. a conservative mutation of one amino acid only may not be substantial) but . **Differences in amino acid sequence should be considered "substantial" if they are linked to the functional characteristics of the protein (the number of different amino acid residues does not matter). Consequently, any difference in amino acid sequence impacting the protein's functionality, as demonstrated by scientific literature, in vitro or in-vivo non-clinical data, should be sufficient to claim a NAS status under indent 1."**	
162 - 164		Comment: Apparent typographical error. We are assuming that the text should	

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		read as amended below. Proposed change: Importantly, changes introduced in the basic structural element should be substantial to warrant a conclusion of NAS (e.g. a conservative mutation of one amino acid only may not be substantial). ~~but,~~ When claiming NAS status, the applicant may therefore need to justify why a given change to the basic structural element is considered substantial.	
172-175		Comment: Please refer to the general comments "Importance of regulatory consistency for the criteria under indent 1" Proposed change: "However, where a molecular structure with the same basic structural element is produced but has additional post-translational modifications, such a structure would likely be considered as 'known active substance' unless it can be shown that these modifications have a significant ~~clinical impact in terms of safety and/ or efficacy.~~ **effect on the functional characteristics of the active substance. This effect can be demonstrated on the basis of scientific literature, in vitro or in-vivo non-clinical data, to support a NAS claim under indent 1.** ~~See Section 3.2 on Third indent below.~~"	
176-181		Comment: Please refer to the general comments "Importance of regulatory consistency for the criteria under indent 1". If each change is assessed in isolation, then each may be considered insubstantial, which would lead to a conclusion that NAS is not justified under the first indent. It is often the combination of changes that makes a molecule significantly different from another molecule as evidenced by pre-clinical data. For example, in respect of incretin memetics, it can be a combination of changes to the primary amino acid sequence and conjugation and position of additional molecular structures that renders the molecule significantly different in terms of activity at its target. Such pre-clinical data is typically used to convince regulators that the medicinal product warrants clinical investigation.	

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		The same data may also be used to justify the innovativeness and thus patentability of the molecule at the European Patent Office. If pre-clinical data demonstrates that changes to the molecular elements change the activity substantially at the target, then such data in combination with the structural changes should be sufficient to justify NAS status. Proposed change line 175: "Where additional molecular structures are chemically attached as part of the downstream manufacturing process, i.e. covalently bound, with or without a linker to the basic structural element, the whole molecule would likely be considered as 'known active substance', irrespective whether the additional structures are located at different positions within the same basic structural element, unless it can be shown that these modifications result in a significant ~~**difference in terms of safety and/or efficacy. See Section 3.2 on third indent below.**~~ **effect on the functional characteristics of the active substance. This effect can be demonstrated on the basis of scientific literature, in vitro or in-vivo non-clinical data, to support a NAS claim under indent 1."** Add the following on page 6/15, line 191: **"As above, appropriate pre-clinical data that demonstrates significant differences relative to the previously approved medicinal product(s) would generally be considered sufficient to justify NAS status."**	
190 - 191		Comment: Any biologics-based conjugate is formed by multiple molecular elements making a fundamental contribution to the pharmacological/immunological/metabolic action. Therefore, such entities should be evaluated as a whole. The reflection paper mentions as an example that the same reasoning can be applied to conjugated vaccine antigens. Fusion proteins and protein-FC conjugates should also be added as relevant example. Proposed change: "The same reasoning can be applied **to any other biologics-based conjugate, such a fusion proteins, protein-FC conjugates** and conjugated	

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		vaccine antigens."	
206 and 210		Comment: For the NAS claim under indent 3, it should not be required that the biological substance impact both the safety and the efficacy. Proposed change: "…. impact on safety and **/ or** efficacy."	
209		Comment: Please refer to the general comments "Level of evidence for indent 3:". Proposed change: "A third indent NAS claim should follow a two-step justification. Firstly, the active substance and its difference with previously authorised active substances should be unequivocally defined. Secondly, it should be demonstrated that due to the differences identified, the active substance has a significantly different safety and efficacy profile compared to active substance(s) contained in EU authorised medicinal product(s). **For biological medicines that are intended for patients that suffer from rare diseases, the justification of a significant difference in safety and / or efficacy profile should be based on plausible scientific grounds, e.g., on the basis of information that is publicly available or otherwise accessible to the applicant, such as scientific literature, and/or available data (not necessary clinical data, in particular a head-to-head trial demonstrating statistical clinical superiority). Clinical data may be used, if available, but the generation of clinical data is not a priori required."**	
207-211		Comment: The reflection paper should also acknowledge that a significantly improved dosing and/or administration scheme supporting an improved patient compliance can support a NAS claim under indent 3. Proposed change:	

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		"Secondly, it should be demonstrated that due to the differences identified, the active substance has a significantly different safety and efficacy profile compared to active substance(s) contained in EU authorised medicinal product(s). **This can also include a significant improvement in clinical PK/PD that would translate to benefits such as an optimised dosing and/or administration scheme supporting an improved patient compliance."**	
212-221		Comment: Please refer to the general comments "Importance of regulatory consistency for the criteria under indent 1". Proposed change: Move this paragraph to indent 1 section. "The claimed differences in quality attributes must be unequivocally defined for a NAS claim to be valid. These differences in quality attributes could include post translational modifications such as glycosylation, sulfatation, phosphorylation or disulphide bridging, or the addition of a functional structure such as polyethylene glycol. Differences in the source of material or manufacturing process should result in clearly defined differences in quality attributes. For example, a different expression system could result in changes to the active substance glycosylation profile which might ~~significant difference in the product safety and/or efficacy profile.~~ **have a significant effect on the functional characteristics of the active substance.** To substantiate such claim, a wide range of sensitive analytical methods should be applied to demonstrate that such claimed differences in quality attributes, as compared to the active substance(s) contained in corresponding EU authorised medicinal product(s), are consistently present, i.e. is not due to batch-to-batch variability."	
232-239		Comment: The draft guidance cross-references another guidance (Line 236) that is not appliable to biological products regarding the type of evidence required to show differences in safety and/or efficacy.	

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		Proposed change: Recommendation is to remove the cross-reference to Section 2.2 "Type of evidence required to show differences" of 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" (EMA/651649/2010) and include any relevant information from that guidance in this guidance to ensure it is a stand-alone document.	
267-269		Comment: Recommend to further clarify if recognized different cell types in the majority of the cases would be regarded as different NAS, from the point of view that a cell as a whole is regarded as the basic structure. Two different cell types with different receptors or mechanism of actions being regarded as the same NAS would likely be more an exception. Proposed change: "A difference in cell type as active substance, such as mesenchymal stem cells (MSCs) versus hematopoietic stem cells (HSCs) or T-lymphocytes versus B lymphocytes **should be sufficient to** ~~**could be considered a difference that could**~~ justify a first indent NAS claim. Differences in cell types considered impurities should not justify a first indent NAS claim"	
271		Comment: Please clarify if this is this intended to be read as differences in the cell source for the same cell type? Proposed change: "ii Different cell source **for the same cell type:** Certain differences in the cell source **for the same cell type**, such as in the case of primary cells vs. cell lines, or tumour cell line vs. non-tumour cell line could be considered differences that could justify a first indent NAS claim."	
271-273		Comment: It is unclear what is the extent of the concept "source" of a cell in this context. In our view a donor is also a source.	

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		Proposed change: Recommend adding also the classification or clarification for pre-selected donors (e.g. donors that have (had) a certain medical condition or have certain genetic features leading to demonstrated changes in certain cells)	
292		Comment: Donors can be healthy subjects. Proposed change: *"Different cell composition:* A difference in the ratio of different related cell-types that are part of the active substance (e.g. CD4+/CD8+ or CD34+ subpopulations) could be considered a difference that could justify a first indent NAS claim, provided that the cellular composition is controlled within a range that is defined by the manufacturing process rather than by ~~patient to patient~~ **donor to donor** variability and impacts in a substantial manner the biological or functional characteristics of the active substance"	
307		Comment: In this section, it should be specified that comparison versus corresponding recombinant protein potentially already approved in EU should be irrelevant Proposed change: To add: **"Comparison between the resulting protein of a gene therapy to related recombinant protein that has already been granted Marketing Authorization in EU would not be required to justify claim under indent 1."**	

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308-309		Comment: Regarding the sentence "(to the extent that is technically possible to define basic structural features) in basic structural elements," it is unclear what is regarded as a basic structural feature in this context. Proposed change: Add example of a basic structural element that can be used under indent 1.	
349-351		Comment: Section 4.3.2 indicates that "When a NAS claim is made on the basis of indent 3, the applicant should justify how the differences in molecular structure, nature of the source material or manufacturing process of the active substance may significantly impact on the safety and/or efficacy profile.". The examples provided for ATMP products in section 4.3 should align with the level of requirements. It is felt that it is not strictly aligned for the example related to differences in cell isolation or selection procedure Proposed change: "differences in cell isolation or selection procedure that lead to improved consistency in composition of the active cell population that is relevant to, and **may** significantly impact, the safety and/or efficacy"	
360		Comment: Propose addition of reference to utilisation of prior knowledge (per **bold text** below): Proposed change: "The claim of substantial differences in the biological characteristics and/or biological activity and/or (to the extent that is technically possible to define basic structural features) in basic structural element, of the active substance should be based on analytical data or plausible scientific grounds, e.g. on the basis of information that is publicly available or otherwise accessible to the applicant, such as scientific literature as well as **other sources of prior**	

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		knowledge. Generation of clinical data is not required."	
376		Comment: Propose addition of reference to utilisation of platform data (per **bold text** below): Proposed change: "As in the case of a NAS claim under indent 1, this justification should be based on plausible scientific grounds, e.g., on the basis of information that is publicly available or otherwise accessible to the applicant, such as scientific literature, and/or available data **such as other sources of prior knowledge**. Clinical data may be used, if available, but the generation of clinical data is not a priori required."	
393 -396		Comment: A monoclonal antibody targeting an antigen already targeted by a monoclonal antibody approved in EU should be NAS under indent 1 if the amino acid sequences of the variable regions are different. Indeed, monoclonal antibodies targeting the same antigen can target different epitopes of this same antigen and have different variable regions. Proposed change: "A monoclonal antibody could be considered a new active substance in itself (first indent) if there is any difference in the amino acid sequence of the variable regions, compared to other monoclonal antibodies. **A difference in amino acid sequence of the variable region can also apply to monoclonal antibodies targeting the same antigen as the one targeted by a monoclonal antibody already approved in EU, which can be eligible to NAS status under indent 1.** Mutations to the constant regions (while keeping the CDR unchanged) would likely be considered not substantial, unless this mutation results in different binding to Fc-receptors."	
394-395		Comment: Clarification is necessary on the given example because mutations of some Amino Acids (AA) in the constant part may modify the binding to the Fc-	

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		receptors without impacting the functionality. Therefore, demonstration of changes in the functionality related to mutation to the Fc region should be demonstrated to support indent 1. Proposed change: "mutations to the constant regions (while keeping the CDR unchanged) would likely be considered not substantial, unless this mutation results in ~~e.g.~~ different binding to Fc-receptors **and different demonstrated functionalities. Such mutations to Fc region impacting the functionality would likely support a NAS claim under indent 1**."	
402-405		Comment: A number of Q&As in this section are unclear. For example, in respect of Qs 3 and 5, would an active substance conjugated to a Fc or a fatty acid rather than a PEG be considered to be a NAS under the first indent? Would it matter if the Fc or fatty acid was conjugated at a different position on the peptide? This is the level of granularity that is required in the guidance document to provide adequate guidance to applicants. See comments above in respect of 155-167 and 384-401 Proposed change: Q2 on lines 402-405 on page 12/15 to be re-phrased as follows: **"Would an active substance derived by recombinant DNA technology be automatically granted new active substance status if a medical product containing the active substance derived from a natural source is already authorised in the EU?"**	
458-459		Comment: A number of Q&As in this section are unclear. This is the level of granularity that is required in the guidance document to provide adequate guidance to applicants. See comments above in respect of 155-167 and 384-401.	

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		Q7 on lines 458-459 on page 12/15 to be re-phrased as follows: **"Would the presence of a protein variant (due to misincorporation), alongside the desired protein, in the medicinal product justify eligibility for NAS?"**	
468		Comment: We recommend including the definition of ATMP in the same way as is done for Biological substance Proposed change: Add definition of ATMP referring to Regulation EC 1394/2007, article 2.1.	
463		Comment: The draft reflection paper refers to a substantial difference of mRNA sequence (protein encoding or regulatory/untranslated) to define a new active substance. There are no criteria to define "substantial". Proposed change: "Yes, provided sufficient evidence is submitted that the differences in the mRNA sequence are substantial. **A substantial difference should be associated with the expression level, or stability of the target antigen/protein. The number of different nucleotides in an mRNA sequence is not material to support the substantial difference. Therefore, any difference in nucleotide sequence intended to support an improved expression or stability, and hence improved immunogenicity, should be sufficient to claim for a NAS status under indent 1.**"	
476		Comment: The definition for basic structural element seems to be leaning more towards description of a biological than towards ATMPs. Proposed change: "Basic structural element **for biologic substances (excluding ATMPs)**"	

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490- 491		Comment: Idem as for 476. It is unclear how to read the concept of "adding" in case of an ATMP. Proposed change: "A molecular structure that is added to the basic structural element and is significantly contributing to the functional (molecular) structure of the active substance **(excluding ATMPs)."**	

Please add more rows if needed.