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Reflection paper on criteria to be considered for the evaluation of new active substance (NAS) status of biological substances

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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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Executive Summary

This document is intended to reflect the current experience of the Biologics Working Party (BWP) of the Committee for Medicinal Products for Human Use (CHMP), the Committee for Advanced Therapies (CAT), and the Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh) on New Active Substance (NAS) in the context of scientific advice and assessment of Marketing Authorisation Applications (MAA). It applies to all types of procedures for submission of a MAA, i.e. Centralised Procedure (CP), Mutual Recognition Procedure (MRP)/Decentralised Procedure (DCP) and purely national procedures for biological and biotechnology-derived medicinal products for human use.

1. Introduction

This document intends to clarify the elements that may be considered in support of a NAS claim for a biological active substance. It does not cover every possible scenario, and therefore applicants are invited to seek scientific advice on the evidence that may be appropriate to substantiate a NAS claim, especially for scenarios not covered in this reflection paper.

The assessment of NAS concerns the active substance contained in the finished medicinal product and not the finished medicinal product in itself (i.e., the finished product composition is not considered).

The NAS assessment is without prejudice to the CHMP opinion on the eligibility to the CP, or to differences in terms of International Non-proprietary Name (INN) of active substances in authorised, or previously authorised, medicinal products. Submitting a MAA under Article 8(3) of Directive 2001/83/EC does not automatically confer a NAS status, nor does submitting through the centralised route. NAS claims can only be considered in the context of the assessment of a MAA.

The outcome of a NAS assessment has no retrospective impact on the eligibility granted to the CP. Applicants are invited to consult the 'pre-submission guidance' on the EMA website for further details on the eligibility for access to the CP.

1.1. Scope

This document describes the current scientific thinking applied to NAS assessment of biological active substances and provides guidance on the elements required to be submitted by applicants to substantiate a NAS claim.

Advanced Therapy Medicinal Products (ATMPs) are within the scope of this document. The different considerations that apply to the NAS assessment of active substances in this class of products are presented separately.

Chemical active substances and radiopharmaceutical medicinal products are excluded from the scope of this reflection paper. Further guidance on the chemical active substances can be found in two reflection papers [EMA/651649/2010 and EMA/CHMP/QWP/104223/2015].

1.2. Relevant guideline

The assessment of NAS claims is guided by the definition of new active substance in Annex I of Chapter 1 of Volume 2A of the Notice to Applicants (NtA), according to which "[a] *new chemical, biological or radiopharmaceutical active substance includes:*

- *a chemical, biological or radiopharmaceutical substance not previously authorised in a medicinal product for human use in the European Union;*
- *an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised in a medicinal product for human use in the European Union but differing significantly in properties with regard to safety and/or efficacy from that chemical substance previously authorised;*
- *a biological substance previously authorised in a medicinal product for human use in the European Union, but differing significantly in properties with regard to safety and/or efficacy which is due to differences in one or a combination of the following: in molecular structure, nature of the source material or manufacturing process;*
- *a radiopharmaceutical substance which is a radionuclide, or a ligand not previously authorised in a medicinal product for human use in the European Union, or the coupling mechanism to link the molecule and the radionuclide has not been authorised previously in the European Union".*

The above first and third indents of the NtA definition for NAS are relevant for new biological active substances. A substance is considered as NAS as long as one of the criteria is fulfilled.

2. General considerations for assessment of biological New Active Substance

To allow for a NAS assessment, the active substance needs to be clearly defined. The claim for NAS should be aligned to what is declared in the MAA dossier, i.e. the administrative section and Module 3.2.S.

2.1. Definition of Active Substance

According to Article 1(3a) of Directive 2001/83/EC, active substance is defined as "any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis".

The Directive further defines in Annex I, Part I, Section 3.2.1 "biological [active] substance" as a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control (see Glossary for further details).

As a general principle, for well-characterised and highly purified active substances, the main component serves as the basis for the substantiation of a NAS claim, and it is normally sufficient to compare its basic structural elements (see Glossary). However, for less well-characterised proteins, complex mixtures of biological active substances, or certain classes of biologicals (e.g. vaccines, plasma-derived products, low molecular weight heparins), the assessment of differences in the basic structural element(s) may require additional considerations, as applicable. These active substances contain several molecular species which are all related to the intended molecular entity, i.e. besides the main molecular entity, other active structurally related entities or isoforms (product related substances) may be present.

The principle outlined above as regards the basic structural element(s) would generally apply to different classes of biological substances. In the case of ATMPs, an adapted approach should be applied, having regard to the specific characteristics of these products. ATMPs are therefore discussed separately (section 4).

2.2. Toolbox approach

It is the responsibility of the Applicant to provide a satisfactory scientific and robust substantiation for a NAS claim. This document discusses tools which may be used to support such a claim. An Applicant is not required to address each and every aspect that this reflection paper presents. If one 'tool' suffices to support the NAS claim, then other tools are not considered necessary. For example, if it is demonstrated that the amino acid sequence is different from any active substance authorised in an EU medicinal product ('first indent claim' from the above-quoted definition in Annex I of Chapter 1 of Volume 2A of the NtA), this would likely constitute sufficient substantiation and further arguments (e.g. claimed clinical benefits based on different manufacturing process, 'third indent claim') are superfluous.

2.3. Other general considerations

It is emphasised that product or process related impurities and extraneous agents (potentially being present) are not considered in the assessment of the NAS claim, whilst they may be relevant for the benefit/risk evaluation of the medicinal product in the context of a MAA. The Q&A contains a list of examples that provide some general guidance. For cases not covered by this Reflection Paper, companies are recommended to seek further scientific advice from the competent authorities.

3. Active substances derived by recombinant or non-recombinant systems (excluding-ATMPs)

3.1. Considerations for New Active Substance assessment based on first indent of NtA definition of NAS

First indent of the NtA definition of NAS: "a chemical, biological or radiopharmaceutical substance not previously authorised in a medicinal product for human use in the European Union".

The first indent addresses the structure of the active substance in itself without considering the need to provide evidence of differences on safety and efficacy. A biological active substance that is not previously authorised in a medicinal product for human use in the European Union and that is from a 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 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.

The therapeutic moiety comprises one or more basic structural elements.

Examples of such basic structural element(s) are the filgrastim part of a PEG-filgrastim or the FVIII part in a FVIII-Fc conjugate (Q&A provides further examples). A biological molecular entity showing differences in this basic structural element(s) would likely be considered a NAS.

For proteins, the amino acid sequence would be considered as the basic structural element. Proteins showing substantial differences in the amino acid sequence constituting the basic structural element would likely be considered NAS. 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. Supportive data would be expected to include analysis of amino acid alignments (e.g. FASTA file format) between the active substance under assessment and active substance(s) in authorised medicinal product(s) (published or own testing data).

Several classes of biological medicinal products are comprised of a group of related molecules with heterogeneous basic structural elements, heparin being one example. In this case, to support a claim of NAS, changes to the range of the heterogeneous basic structures would need to be shown. This might include additional structures or a change in the relative proportion of the various structures. 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. See Section 3.2 on *Third indent below*.

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*.

For the particular case where the active substance is formed by compounds (molecular entities) that comprise multiple molecular elements, whereby each element constitutes a (potential) active substance in itself, i.e. each element makes a fundamental contribution to the pharmacological/immunological/metabolic action of the molecular entity as a whole, it will be evaluated whether it will qualify as an active substance as a whole entity in itself or as a combination of active substances. For example, in an antibody-drug conjugate, both the antibody and drug are expected to have a pharmacological/immunological/metabolic action. Whilst the antibody-drug conjugate (as a whole entity) is considered as the active substance, differences in either the antibody or drug should be considered in the assessment and might be supportive of a NAS claim. The same reasoning can be applied to conjugated vaccine antigens.

As noted, biologicals are usually complex mixtures. However, as the NAS is based on the basic structural element, which is expected to be present in most if not all components of the mixture, consideration of the main component or expected (amino acid) sequence would usually be sufficient in the justification of a NAS claim. For example, in the case of the active substance human insulin, the A21 desamido human insulin (which is considered part of the insulin active substance[1]) does not need to be separately taken into consideration in the NAS assessment.

3.2. Considerations for New Active Substance assessment based on the third indent of NtA definition of NAS

Third indent of NtA definition of NAS: "a biological substance previously authorised in a medicinal product for human use in the European Union, but differing significantly in properties with regard to safety and/or efficacy which is due to differences in one or a combination of the following: in molecular structure, nature of the source material or manufacturing process"

A biological substance can still be considered as a NAS even when structural differences are insufficient for a NAS claim under indent 1. In such case, the therapeutic moiety has the same basic structural element(s) but other differences in variability are present and have an impact on safety and efficacy.

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

[1] Ph.Eur. 01/2011;0838

different safety and efficacy profile compared to active substance(s) contained in EU authorised medicinal product(s).

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 lead to a significant difference in the product safety and/or efficacy profile. 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.

As noted in section 2, a biological active substance can be a complex mixture of a main component and/or several product related substances. Meaningful changes within the exact composition of such a complex mixture (e.g. complete afucosylation of a monoclonal antibody instead of the presence of both fucosylated and afucoslyated forms) could be considered sufficient to justify the granting of NAS status, if it is substantiated that it translates in significant difference (e.g. in afucosylation) in terms of efficacy and/or safety.

In summary, claims of NAS linked to structural difference of the substance insufficient for a NAS claim under indent 1 shall be justified under this indent and require evidence of significant differences in properties with regard to efficacy and/or safety compared to the active substance(s) contained in EU authorised medicinal products.

Despite not being generally applicable to biological medicinal products, relevant guidance on the type of evidence required to show differences in safety and/or efficacy compared to the active substance(s) contained in medicinal products already authorised in the EU, as well as on what might constitute a significant difference in safety and/or efficacy to justify the designation of the active substance as NAS, can be found in 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). Examples of such clinically relevant differences quoted in this reflection paper include changes to the overall efficacy at clinically relevant doses, clinically relevant changes that result in significant differences to contraindications, warnings or clinically significant adverse reactions, clinically relevant changes that affect significantly drug:drug interactions such that the population able to take the drug is significantly different, clinically relevant changes that allow the product to be used in a wider patient population within the current indication or previously excluded sub-groups.

The aforementioned reflection paper also acknowledges that compelling non-clinical data may support relevant substantial differences in safety and/or efficacy, where it is not feasible to conduct head-to-head clinical studies.

4. Advanced Therapy Medicinal Products (ATMPs)

This section is aimed at providing guidance for supporting a NAS claim for ATMPs based on the first or third indent of the above referenced NtA NAS definition. In both cases, the NAS claim should be based on differences in active substance. Differences in process- and product-related impurities or extraneous agents are not considered for a NAS claim.

4.1. Considerations for New Active Substance assessment based on first indent of NtA definition of NAS

For ATMPs, it may be technically difficult to identify the basic structural features. For this reason, under indent 1, the consideration whether an active substance constitutes a NAS could be based on its biological characteristics and/or biological activity. However, to the extent that the basic structural element of the active substance in an ATMP can be defined, differences in the basic structural element compared to active substance(s) authorised in the EU could support a NAS claim.

The following illustrative differences in active substance can justify a NAS claim under indent 1.

4.1.1. Cell-based and tissue engineered products

A first indent NAS claim could be justified by substantial differences in biological characteristics and/or biological activity and/or (to the extent that is technically possible to define basic structural features) in basic structural elements, of the active substance, including differences caused by a difference in starting materials or manufacturing process. The following is a non-exhaustive list of examples:

i. *Different cell type*: 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 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.

ii. *Different cell source*: Certain differences in the cell source, 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.

Differences in the source of starting material used for the manufacturing of MSCs (e.g., placenta, adipose tissue, umbilical cord blood, or bone marrow) could justify a first indent NAS claim as they could be considered to cause substantial differences in the biological characteristics and/or biological activity of the active substance. In contrast, it cannot be assumed that a difference in the source material used for manufacturing HSCs (i.e., bone marrow or mobilised peripheral blood) impact *a priori* on biological characteristics and/or biological activity of the active substance. It follows that, in case of HSCs, a first indent NAS claim based on a difference in the source material should be supported by a product-specific justification that such changes result in substantial differences in the biological characteristics and/or biological activity of the active substance.

It is stressed that the mere change of cell stock, or in case of a different donor for primary cells (as in an autologous or matched-donor scenario) does not justify a NAS claim, unless evidence of a substantial change in the biological characteristics and/or biological activity of the active substance can be demonstrated.

iii. *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 variability and impacts in a substantial manner the biological or functional characteristics of the active substance.

iv. *Differences in other biological characteristics*: A difference in the activation or differentiation status of the cells could be considered a difference that could justify a first indent NAS claim,

provided that this property is substantial for the biological characteristics and/or biological activity of the active substance.

v. *Differences in manufacturing process:* The following is a non-exhaustive list of examples of differences in manufacturing process that could justify a first indent NAS claim, provided that the difference in manufacturing process has a substantial impact on biological characteristics and/or biological activity of the active substance.

- Non-cultured cells vs. cultured cells.
- Selective stimulation during cell culture by inclusion of growth factors or cytokines
- Dendritic cells activated with a tumour lysate vs. dendritic cells activated by means of purified tumour protein,
- Bioprinting of the active substance vs. conventional tissue engineering methods.

4.1.2. In vivo gene therapy

A first indent NAS claim could be justified by substantial differences in biological characteristics and/or biological activity and/or (to the extent that is technically possible to define basic structural features) in basic structural elements, of the active substance, including differences caused by the manufacturing technology. The following is a non-exhaustive list of examples:

i. *Differences in the transfer system*: A difference in the transfer system when being part of the active substance (e.g. viral vector system vs. non-viral vector system) is expected to be a substantial difference that could justify a first indent NAS claim.

ii. *Differences in the viral vector*: A difference in the viral vector (e.g. adenovirus vs. AAV) is expected to be a substantial difference that could justify a first indent NAS claim.

In addition, a difference in virus capsid due to the use of a different (sub-)type of virus vector or the presence of different capsid proteins is expected to be a substantial difference that could justify a first indent NAS claim.

The above examples are not exhaustive, other substantial differences in the viral sequence (e.g. differences that reduce the risk of insertional mutagenesis or the risk of formation of replication competent viruses, as well as differences associated with the integration profile) could also justify a first indent NAS claim.

iii. *Differences in the therapeutic sequence:* A difference in the therapeutic sequence resulting in a substantial difference in amino acid sequence of the therapeutic protein could justify a first indent NAS claim.

In addition, other differences in the therapeutic sequence that substantially impact on the biologic characteristics and/or biological activity of the therapeutic protein could justify a first indent NAS claim. Differences in the therapeutic sequence that substantially impact the level of expression or stability of the therapeutic protein could justify a first indent NAS claim.

iv. *Differences in the regulatory sequences*: Differences in the regulatory sequences that substantially impact the level of expression of the therapeutic protein, stability, tissue tropism or transduction efficiency could justify a first indent NAS claim.

v. *Differences in manufacturing technology*: Differences in manufacturing process that have a substantial impact on biological characteristics and/or biological activity of the active substance could justify a first indent NAS claim. For example, due to the different precision, efficiency,

and specificity profiles of the different nuclease-based engineering technologies, the various technologies are considered to likely substantially impact on biological and functional characteristics of the active substance and thus could justify a first indent NAS claim.

4.1.3. Genetically modified cells

A 1st indent NAS claim could be justified by substantial differences in biological characteristics and/or biological activity and/or (to the extent that is technically possible to define basic structural features) in basic structural elements, of the active substance, including differences caused by the manufacturing technology. The following is a non-exhaustive list of examples:

i. *Differences in cells*: As genetically modified cells are also cell-based products, considerations as described above for cell-based products apply.

ii. *Differences in therapeutic sequence*: considerations as described above for *in vivo* gene therapy products apply.

iii. *Differences in regulatory sequences:* Differences in the regulatory sequences that substantially impact the level of expression, function or stability of the therapeutic protein could justify a 1st indent NAS claim.

iv. *Differences in the viral vector (starting material):* Differences in the viral vector that have a substantial impact on biological characteristics and/or biological activity of the active substance could justify a 1st indent NAS claim. The following is a non-exhaustive list of examples that could justify a NAS claim:
   - differences in the viral vector used to transduce the cells (e.g. retrovirus vs. lentivirus);
   - differences at the level of the viral sequence that reduce the risk of insertional mutagenesis or the risk of formation of replication competent viruses in the transduced cells;
   - differences associated with the integration profile in the transduced cells;
   - differences at the level of the virus capsid or viral sequence that impact the transduction profile or composition of the transduced cell population.

v. *Differences in manufacturing process:* Differences in manufacturing process that have a substantial impact on biological characteristics and/or biological activity of the active substance could justify a 1st indent NAS claim. For instance, the use of different nuclease-based engineering technologies (e.g. zinc finger vs Cas9) is expected to have a substantial impact and could justify a 1st indent NAS claim, even if they target the same DNA sequence.

4.2. Considerations for New Active Substance assessment based on the third indent of NtA definition of NAS

A NAS claim based on the third indent of the above referenced NtA NAS definition should be considered where a related active substance has been previously authorised in a medicinal product in the EU but differs significantly in properties with regard to safety and/or efficacy, due to differences in molecular structure, nature of the source material or the manufacturing process.

The following examples could justify a NAS claim under indent 3:

- using autologous vs. allogeneic cells, as the nature of the starting material is expected to significantly impact the safety and/or efficacy.

- differences in cell isolation or selection procedure that lead to improved consistency in composition of the active cell population that is relevant to, and significantly impacts, the safety and/or efficacy

difference in the manufacturing process that permit expanding the treatable population (within the same targeted therapeutic indication).

4.3. Level of evidence

4.3.1. NAS claim under indent 1

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 available data. Generation of clinical data is not required.

It is noted that a single substantial difference in biological characteristics, biological activity and/or (to the extent they can technically be defined) basic structural element is sufficient to justify a NAS claim. One clear-cut and convincing justification is sufficient. For example, in the case of cells transduced with different viral vectors, the applicant is not expected to demonstrate that, in addition of the relevant differences linked to the vector, there are also relevant differences at the level of the therapeutic and/or regulatory sequences. Moreover, in cases where it is possible to identify relevant differences in basic structural elements, the applicant could justify a NAS claim on the basis of these differences, without having to demonstrate substantial differences in biological characteristics and/or biological activity. For example, in the case of CAR-T-cells, the applicant may choose to justify a NAS claim on the basis of relevant differences in the CAR construct.

This document contains a list of possible differences that may justify a NAS claim to guide applicants (toolbox).

4.3.2. NAS claim under indent 3

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. Clinical data may be used, if available, but the generation of clinical data is not a priori required.

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.

5. Q & A for new active biological substance

This Q&A provides additional elements complementing Section 3 of this Reflection Paper. Examples related to ATMPs have been provided in Section 3.

1. For biological active substances derived by recombinant DNA technology could a different amino acid sequence substantiate a new active substance claim?

Yes, for biological active substances derived by recombinant DNA technology, a different amino acid sequence in the basic structural elements could justify the status of a new active substance, provided

that the change is considered substantial (e.g. not a 'conservative substitution'). The Applicant may need to justify that the differences in amino acid sequence are substantial in order to warrant a conclusion of NAS (first indent NtA definition).

Example:

A monoclonal antibody could be considered a new active substance in itself (first indent) if the amino acid sequence is substantially different compared to other monoclonal antibodies; 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.

If a B-domain deleted coagulation factor FVIII (which constitutes a major difference when compared to the basic structural element of the native full length factor FVIII) were to be submitted it would likely be considered new active substance when its amino acid sequence, i.e. the basic structural element, is substantially different from the amino acid sequence of the active substance already authorised in the EU (first indent NtA).

2. Would an active substance derived by recombinant DNA technology, automatically be granted the status of a new active substance, if such an active substance, but derived from a natural source, is already present in an EU authorised medicinal product?

No. Biological active substances derived by recombinant DNA technology products will not automatically be considered a new active substance versus an authorised active substance derived from a natural source authorised in the EU. In case it is demonstrated that these active substances differ significantly in properties with regard to safety and/or efficacy due to differences discussed in Section 3.2 **Error! Reference source not found.**of the present reflection paper, the biological active substance derived by recombinant DNA technology could be considered NAS under the third indent.

It should be noted that potential differences in viral safety are not considered in the assessment of NAS because these are not due to the properties of the active substance of the medicinal product.

Example:

If a recombinant coagulation factor active substance was to be submitted for the first time and a plasma-derived version of the same coagulation factor active substance was already authorised in the EU, it would not be considered a new active substance, except if these active substances differ significantly in properties with regard to safety and/or efficacy (third indent NtA definition). In such case the recombinant coagulation factor could be considered NAS.

3. a. Would a pegylated version of an existing active substance be considered a new active biological substance?

If the basic structural element (the protein part) of the pegylated version would be the same as for the active substance previously authorised in the EU, the pegylated version would not *per se* be considered NAS under the first indent of the NtA definition. However, the pegylated version of an active substance could be considered as a NAS provided the pegylation of the basic structural element would lead to properties differing significantly with regard to safety and/or efficacy (third indent NtA definition).

3. b. Is it possible for a second pegylated version of a pegylated active substance to be considered a New Active Substance?

A second pegylated version of a pegylated active substance could still be eligible for NAS status. For example, in case the PEG element would be attached at a different position of the amino acid sequence, i.e. the basic structural element, or the PEG element would differ in size, and result in a

substance differing significantly in properties with regard to safety and/or efficacy, it could be considered a NAS (third indent NtA definition).

4. Would a vaccine antigen produced from a new viral or bacterial strain be considered to be a new active biological substance?

Yes, a vaccine antigen produced from a new viral or bacterial strain would likely be considered to be a new active substance. This is without prejudice to Articles 12, 13f, 18 and 21 of Regulation (EC) No 1234/2008.

5. Would a second conjugated versus an authorised conjugated vaccine antigen be considered to be a new active biological substance when using a different carrier molecule?

Yes. Due to the difference in carrier structure (which has a immunological action in itself), the second conjugated vaccine would likely be considered NAS (first indent NtA definition).

Example:

If an antigen was to be prepared by conjugation with CRM_{197} and the authorised antigen was conjugated to a tetanus toxoid, the CRM conjugated antigen would likely to be considered a NAS.

6. Would a version of an existing biological active substance produced by a different manufacturer using a different process be considered as new active biological substance?

An evaluation of the specific scenario is needed. A difference in manufacturer and/or differences in the manufacturing process would in itself not be sufficient to grant New Active Substance status.

If the change in manufacturing process would result in significantly different properties with regard to safety and/or efficacy, the active substance could be considered NAS (third indent NtA definition).

Examples:

Authorised Biosimilar Medicinal Products may be from different manufacturers and/or produced using different manufacturing processes, however they have shown not to have significant differences in terms of safety and/or efficacy vis-à-vis the reference medicinal product.

7. Would the presence of a protein variant (due to misincorporation) in addition to the desired protein, could qualify as a NAS ?

No. It is acknowledged that due to misincorporation (especially under limited feeding conditions) variants may be present at levels of a few percent, where amino acids substituted. These would likely be qualified as product related substances in the total mixture which constitutes the active substance.

8. For biological active substances comprising mRNA, would a difference in the mRNA sequence (protein encoding or regulatory/untranslated) be considered a new active substance?

Yes, provided sufficient evidence is submitted that the differences in the mRNA sequence are substantial.

6. Glossary

Active substance

Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis, as provided by Article 1(3a) of Directive 2001/83/EC.

Basic structural element

The core structure of the active substance without added functional molecular structures or other structures that are added, for example, due to post-translation modifications.

Biological substance

A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control, as provided in Annex I, Part I, Section 3.2.1, of Directive 2001/83/EC. *Please refer also to the CMDh Questions & Answers on Biologicals.*

International Non-proprietary Name (INN)

An International Non-proprietary Name (INN) identifies a pharmaceutical substance or active pharmaceutical ingredient by a unique name that is globally recognised and is public property. A non-proprietary name is also known as a generic name. *Please refer to the Guidance on the use of International Non-proprietary Names (INNs) for pharmaceutical substances (2017), WHO.*

Functional (molecular) structure

A molecular structure that is added to the basic structural element and is significantly contributing to the functional characteristics of the active substance.

New active substance (NAS)

- a chemical, biological or radiopharmaceutical substance not previously authorised in a medicinal product for human use in the European Union;
- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised in a medicinal product for human use in the European Union but differing significantly in properties with regard to safety and/or efficacy from that chemical substance previously authorised;
- a biological substance previously authorised in a medicinal product for human use in the European Union, but differing significantly in properties with regard to safety and/or efficacy which is due to differences in one or a combination of the following: in molecular structure, nature of the source material or manufacturing process;
- a radiopharmaceutical substance which is a radionuclide, or a ligand not previously authorised in a medicinal product for human use in the European Union, or the coupling mechanism to link the molecule and the radionuclide has not been authorised previously in the European Union,

as provided in Annex I of Chapter 1, Volume 2A of the Notice to Applicants.

Process-Related Impurities

Impurities that are derived from the manufacturing process. They may be derived from cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing (e.g., processing reagents or column leachables). *ICH Topic Q6B - Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. CPMP/ICH/365/96.*

Product-Related Impurities

Molecular variants of the desired product (e.g., precursors, certain degradation products arising during manufacture and/or storage) which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety. *ICH Topic Q6B - Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. CPMP/ICH/365/96.*

Product-Related Substances

Molecular variants of the desired product formed during manufacture and/or storage which are active and have no deleterious effect on the safety and efficacy of the drug product. These variants possess properties comparable to the desired product and are not considered impurities. ICH Topic Q6B *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. CPMP/ICH/365/96.*

2. References

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use.
- Notice to Applicants (NtA), Volume 2A — Procedures for marketing authorisation - Chapter 1 marketing authorisation.
- ICH Topic Q 6 B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. CPMP/ICH/365/96
- CHMP 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. 18 October 2012
- Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance (NAS) status of chemical substances. EMA/CHMP/QWP/104223/2015, 17 December 2015.
- CMDh Questions & Answers on Biologicals CMDh/269/2012, Rev. 2