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Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of New Active Substance (NAS) status of chemical substances

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Executive Summary

This reflection paper is intended to reflect the current experience of the Quality Working Party (QWP), of the Committee for Medicinal Products for Human Use (CHMP) and the Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh) concerning the definition of a New Active Substance (NAS) in the context of preparation of dossiers and submissions of applications for Marketing Authorisation (MAA) in the Centralised Procedure (CP), the Mutual Recognition Procedure (MRP)/Decentralised Procedure (DCP) and purely national procedures for chemical medicinal products for human use.

The paper describes the chemical structure and properties criteria to be taken into account by the CHMP to qualify a chemical active substance as NAS, as well as the required elements to be submitted by applicants to substantiate their claims.

1. Introduction

This reflection paper intends to provide clarifications for applicants on the elements to qualify an active substance as NAS in the light of Article 10.2b of Directive 2001/83/EC and the Chapter I - Volume 2A of Notice to Applicants, as well as the evidence required. However it cannot cover every scenario, and therefore applicants are invited to obtain scientific advice for scenarios not covered in this reflection paper.

The above assessment is without prejudice to any assumption at the time of eligibility to the CP, MRP/DCP procedures, or to the grant of an International Non-proprietary Name (INN) by the WHO.

Eligibility to the CP based on the claim that the medicinal product for human use contains a new active substance must be dissociated from the assessment of the scientific data submitted in support of the NAS claim during evaluation of the marketing authorisation application. Agreement on designation as a NAS can only be made after a detailed assessment of the application.

Applicants are invited to consult the 'pre-submission guidance' on the EMA website for further details on the eligibility to the CP.

1.1. Scope

This reflection paper describes the chemical structure and properties criteria to be taken into account to qualify a chemical active substance as NAS, as well as the required elements to be submitted by applicants. It applies to marketing authorisation applications including solely chemical active substance(s) eligible to the centralised and MPR/DCP and purely national procedures.

Biological and biotechnological active substances and active substances to be included in radiopharmaceutical medicinal products are excluded from the scope of this reflection paper.

1.2. Legal basis and relevant guidelines

Directive 2001/83/EC

Article 10.2.b of Directive 2001/83/EC states:

"[…] The different salts, esters, ethers, isomers, mixture of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance unless they differ significantly in

properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant […]."

Further information can be found in the Annex 1, Volume 2A, Chapter 1 of the Notice to Applicants (NtA).

2. Discussion and guidance

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 structure of the therapeutic moiety is different from any other authorised so far as a medicinal product for human use.

If the chemical active substance is structurally related as a salt, ester, ether, isomer, mixture of isomers, complex or derivative of an already approved active substance(s) in the European Union, it should be assessed whether it shares the same therapeutic moiety at the site of the biological activity as the already approved active substance and if so whether it differs significantly in properties with regard to safety and/or efficacy.

Guidance is provided below to define the elements taken into account to qualify an active substance as salt, ester, ether, isomer, mixture of isomers, complex or derivative of another one in the context of the NAS status claim.

2.1. Isomers

Isomers should in this context be understood as enantiomers. Other types of isomers are presumed not to share the same therapeutic moiety unless they are able to isomerise *in vivo*. Stereoisomers related to each other as enantiomers have the same connectivity but are non-superimposable mirror images of each other. This implies that enantiomers have the same chemical and physical properties (except their ability to rotate plane polarized light), i.e. act in exactly the same manner, except when they interact with other chiral structures. In the case one enantiomer is applied for where the other enantiomer is the active substance in a previously authorised medicinal product for human use within the European Union it has to be assessed whether they differ significantly with respect to safety and/or efficacy properties. This assessment will be based on the data provided by the applicant.

When an isomer that is not the enantiomer of an already approved active substance (diastereoisomer, geometrical isomer, regioisomer, constitutional isomer etc.) is applied for it is presumed that it will not expose the patients to the same therapeutic moiety, unless it is able to isomerise *in vivo,* and could be considered as NAS. In such cases, evidence that the substance is not able to isomerise *in vivo* may need to be provided.

2.2. Mixtures of isomers

Where a previously authorised medicinal product for human use in the European Union includes a racemate and a new application for only one of the two enantiomers of the racemate is submitted, this enantiomer would have been a substantial part (50 %) of the racemate and would therefore be considered as the same active substance as the racemic mixture, unless the applicant provides evidence that the two substances differ significantly in properties with regard to safety and/or efficacy.

This does also apply to other situations where mixtures of diastereoisomers or other isomers have been authorised as medicinal products for human use and a new application contains only one of the isomers of the mixture.

2.3. Complexes

The term 'complexes' encompasses several types of structures. Two examples of complexes used as medicinal products for human use can be found below.

a. Complexes intended to release an active substance that is entrapped by the complex in the blood circulation or elsewhere. Examples of such complexes are e.g. piroxicam betadex or nicotine betadex.

b. Another type of complexes is those that are intended to remain intact in the body. There are e.g. a number of gadolinium complexes, with different complexing ligands, and with extremely low dissociation constant. They exhibit their effect by distributing gadolinium to places where it enhances the images obtained by NMR imaging. Due to the toxicity of free gadolinium they are designed to remain intact (not dissociate and release the metal).

Complexes of the category a. above prepared from an already approved active substance are designed to release the original substance *in vivo* and will consequently not be considered as NAS in themselves. Therefore the NAS status will have to be justified by significant differences with regard to safety and/or efficacy. On the contrary, complexes of the category b. exhibit their effect without dissociating, and different ligands may be used to complex the same metal. Because they do not dissociate the therapeutic moieties are presumed to be different and could be considered as NAS. In such cases, evidence that the complex does not dissociate may need to be provided.

2.4. Derivative

The term derivative, in the context of this reflection paper, includes related active substances which expose the patient to the same therapeutic moiety.

This includes notably situations:

a. Where the original substance or its active metabolite(s) *in vivo* will be derived from the new applied substance in such a manner that the patients are exposed to the same therapeutic moiety of the original substance (the applied substance is a prodrug).

b. Where the new applied active substance is the same substance as the therapeutic moiety that the patients were exposed to when treated with the original active substance (the applied substance is a metabolite).

In these situations, substances related as a "derivative" to the active substance of an already approved medicinal product for human use in the European Union will not be confirmed as NAS unless the applicant provides evidence that the substance being evaluated differs significantly in properties with regard to the safety and/or efficacy from the substance already approved.

The above mentioned situations also apply to stereoisomers which isomerise to authorised active substances *in vivo*.

2.5. Esters and ethers

Converting an active substance to certain esters or ethers is a well-established way of preparing so-called prodrugs. The purpose of a prodrug is to deliver the same therapeutic moiety to the patient, possibly with some differences such as a different bioavailability, a different *in vivo* distribution pattern, etc. Such esters or ethers of an already approved medicinal product in the European Union that are designed to be hydrolysed *in vivo* and expose the patient to the same therapeutic moiety as the original active substance will not be considered as NAS unless the applicant provides evidence that the substance being evaluated differs significantly in properties with regard to safety and/or efficacy from the one already approved.

If the applicant provides evidence that an ester or ether of an already approved medicinal product in the European Union exerts its effect in an intact shape (is not hydrolysed *in vivo*), and the patients are not exposed to the same therapeutic moiety as with the already approved medicine it could be considered as NAS. In such cases, evidence that the substance exerts its effect in an intact shape (is not hydrolysed *in vivo*) may need to be provided.

2.6. Salts

Salts usually dissociate in aqueous solution and the therapeutic moiety is no longer associated with the counter ion but is rather surrounded by solvent molecules and ions present in the solution. A different salt of an active substance previously authorised as part of a medicinal product in the European Union would be considered as the same active substance, unless the applicant provides evidence that the substance being evaluated differs significantly in properties with regard to safety and/or efficacy from the one already approved.

2.7. Solid state forms and NAS status

Since cocrystals, hydrates and solvates are held together by weak interactions that usually dissociate in a similar way as salts upon dissolution they will expose a patient to the same therapeutic moiety. As for salts, they will not be considered as NAS unless the applicant provides evidence that the substance being evaluated differs significantly in properties with regard to safety and/or efficacy from the one already approved.

This applies also to morphologically different crystal forms of an active substance. The differences between such polymorphic forms will immediately disappear when dissolved and they will be considered as the same active substances.

2.8. Documentation

Where an applicant submits a claim of NAS in the light of Article 10.2b of Directive 2001/83/EC, the applicant should demonstrate whether the active substance(s) subject of the application shares the same therapeutic moiety as the active substance(s) previously authorised in medicinal product(s) for human use. This should include a demonstration that the administration of the applied active substance would not expose the patient to the same therapeutic moiety as an already authorised active substance in the European Union. It is recommended that this is substantiated by comparison of structural substance/features which can be obtained using established databases and discussion on the therapeutic moieties for any structurally related already authorised substances in relation to the therapeutic moiety of the claimed NAS. Results of such investigations should be provided within the dossier.

When a substance applied for exposes the patient to the same therapeutic moiety as the previously active substance(s) as part of a medicinal product(s) authorised in the European Union, the applicant should provide evidence that the related active substances differ significantly in properties with regard to safety and/or efficacy. The documentation needed for such a claim will be dependent on the particular case details; applicants are advised to seek Scientific Advice accordingly.

3. 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.

Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance (Doc. Ref.: EMA/651649/2010).