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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

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1. Introduction

The scope of this paper is restricted to consideration of differences between a single enantiomer, a complex, a derivative or a different salt or ester and the corresponding reference active substance. The questions being addressed are “when should such an active substance be regarded as a new active substance (NAS) in relation to the relevant reference active substance and what level of evidence would be required to confirm the designation as a new active substance”?

Biological active substances are excluded from the scope of this reflection paper.

The current legislation, Article 10.2.b of Directive 2001/83/EC, as amended, states that *the different salts, esters, ethers, isomers, mixture of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance unless they differ significantly in properties with regard to safety and/or efficacy. 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.*

In addition according to the Notice to Applicant (Volume 2A, Chapter 1), a new chemical, biological or radiopharmaceutical active substance includes:

- *an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product in the European Union but differing in properties with regard to safety and efficacy from that chemical substance previously authorised.*

This reflection paper outlines the scientific approach to evaluate whether enantiomers, complexes, derivatives or different salts or esters of an existing active substance should be considered as a NAS or not. However, it cannot cover every scenario, and therefore applicants are invited to obtain scientific advice for scenarios not covered in this reflection paper.

2. Discussion

This paper aims at providing a harmonised approach to evaluate whether development of enantiomers, complexes, derivatives or different salts or esters of an existing active substance should be considered as a NAS or not for the following reasons:

- To provide a consistent interpretation across Europe, so that mutual recognition, decentralised and centralised procedures can operate effectively;

- To enable industry to have a clear understanding of what will, and what will not constitute a new active substance, such that this can be taken into account when deciding on development programmes and the supporting data package.

Another aspect related to the designation as a new active substance or not is access to or compulsory use of the centralised procedure. The outcome of the assessment on whether such active substance is to be considered as a new active substance compared to the reference active substance has no impact on a previously granted access to the centralised procedure.

It is expected that applicants will provide evidence to justify their claims of NAS status in their submission, taking into account this guidance document.

2.1. Criteria to be applied in deciding on whether an active substance differs significantly with regard to efficacy and/or safety compared to the relevant reference active substance

Ultimately, the decision on whether or not an active substance is sufficiently different from an existing reference active substance will need to be made on a case-by-case basis guided by certain principles:

- The data requirements for marketing authorisation and for determination of whether the differences are sufficient to designate the product as a NAS compared to a reference active substance are not necessarily the same. The scope of this paper is restricted to designation as new active substance and does not address data requirements for marketing authorisation. For the purposes of designation as a NAS only, the default position is that an enantiomer, complex, derivative or a different salt or ester is not different from the reference active substance, unless demonstrated to be otherwise. There is not a *requirement* on applicants to conduct additional studies over and above those required for authorisation, to specifically explore whether the active substance is a NAS or not, however an applicant may *choose* to perform additional studies to demonstrate differences to the reference active substance, and should an applicant not demonstrate the degree of difference required for such a designation, it would not be regarded as a NAS.
- Direct comparison between the enantiomer, complex, derivative or different salt or ester and the reference active substance is the preferred way to demonstrate the differences claimed and to justify designation as a NAS. Indirect, non-comparative evidence may be acceptable, if scientifically justified. However it is noted that indirect, non-comparative evidence may be less compelling.

2.2. Type of evidence required to show differences

The Directive 2001/83/EC refers to significant differences in safety and/or efficacy being required to justify new active substance status vis-à-vis a reference active substance. The most compelling evidence would be clinically relevant human safety and/or efficacy differences. It is therefore preferred that head-to-head clinical studies are conducted where feasible, in order to demonstrate clinically relevant differences in safety and/or efficacy, unless there is compelling evidence derived from pre-clinical and/or other clinical data. In addition the package of data may include pharmacologic or pharmacodynamic studies, animal models of disease, microbiology studies and toxicological studies (if safety differences are anticipated), or other data where these are relevant to reflecting the clinically relevant human difference, or have been conducted as part of the development programme to allow the clinical trial programme to commence. If pre-clinical models are used, it is preferable that the comparison is derived from direct comparative data.

2.3. What might constitute a significant difference in safety and/or efficacy to justify new active substance status?

2.3.1 Evidence likely to be sufficient:

Whilst this would need to be considered on a case-by-case basis, it is anticipated that any of the following might be regarded as sufficiently significant differences:

- Significant changes to the dosing frequency (e.g. bd to od) or another route of administration mandated by significant differences in safety and/or efficacy properties;
- Changes to the overall efficacy at clinically relevant doses (e.g. clinically and statistically significant difference in the primary endpoint);

- Clinically relevant changes that result in 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; such changes may be demonstrated in drug:drug interaction studies;
- Clinically relevant changes that allow the product to be used in a wider patient population within the current indication or previously excluded sub-groups (e.g. the product is to be used in the patient population which previously was excluded due to significant safety concerns or lack of efficacy);
- Compelling preclinical data where it is not feasible to conduct head to head clinical studies, e.g. differences in reproductive toxicity or carcinogenicity, or the reference active substance is not authorised for the proposed indication.

2.3.2 Evidence unlikely to be sufficient:

- Changes to pharmacokinetics alone (that do not alter elements, as outlined in section 2.3.1);
- Preclinical differences that are inconclusive or unlikely to result in significant changes in clinical efficacy or safety;
- Extrapolation between studies (i.e. the claim for significantly different efficacy is based on a study or studies with the reference active substance and a different study or studies with the proposed form): a direct head-to-head comparison is generally preferred in a sufficiently powered study to show a clinically and statistically significant difference;
- The widening of the patient population (either within the current indication, or to a different indication) to groups not previously studied for the reference active substance, if not substantiated with other robust data, as outlined in section 2.3.1.

2.4. Significance of filing route or legal basis of marketing authorisation application

It is the properties of the product, not the filing route or legal basis of the marketing authorisation application that determine whether an active substance is deemed to be a NAS or not compared to a reference active substance. Filing under Article 8(3) of Directive 2001/83/EC, does not automatically confer a NAS status, nor does filing through the centralised route. Agreement on designation as a NAS can only be made after a detailed assessment of the application.

3. Conclusion

This reflection paper presents criteria in deciding on whether the development of an enantiomer, complex, derivative or different salt or ester should be considered as a NAS or not from a scientific viewpoint, with the intention of achieving a harmonised approach across the centralised and national/MR/DCP procedures. It is also considered that such determinations/opinions should be made at the time of first authorisation, agreed at a European level, and published in the relevant Public Assessment Report.

4. 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.

Volume 2A – Procedures for marketing authorisation - Chapter 1 marketing authorisation