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Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer) as new active substance in relation to a reference active substance which is a racemic mixture of enantiomers

Draft

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7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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1. Introduction

The scope of this paper is restricted to consideration of differences in isomeric composition of a product compared to a racemic reference active substance. The question being addressed is “when should an enantiomer be regarded as a new active substance (NAS) in relation to a reference active substance which is a racemate and what level of evidence would be required to confirm the designation as a new active substance”?

According to 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:

- a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product in the European Union;
- 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;
- a biological substance previously authorised as a medicinal product in the European Union, but differing in molecular structure, nature of the source material or manufacturing process;
- a radiopharmaceutical substance which is a radionuclide, or a ligand not previously authorised as a medicinal product in the European Union, or the coupling mechanism to link the molecule and the radionuclide has not been authorised previously in the European Union.

2. Discussion

An appropriate designation as a new active substance is critical as this has some regulatory consequences. Indeed designation as a new active substance will mean that the medicinal product will not be part of the same global marketing authorisation as the initial authorisation for data exclusivity purposes. It is therefore of importance to have a harmonised approach on the interpretation of the legislation for two reasons: one to provide a consistent interpretation across Europe, so that mutual recognition, decentralised and centralised procedures can operate effectively. The second reason is 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.

2.1. Criteria to be applied in deciding on whether a single enantiomer differs significantly with regard to efficacy and safety compared to the racemic reference product

Ultimately, the decision on whether or not a single enantiomer is sufficiently different from an existing reference active substance will need to be made on a case-by-case basis however some principles can be applied:

- The data requirements for licensing 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. Whilst from a development point of view it would be most beneficial if one package addressed both needs, a package of data may be sufficient for licensing purposes but may not adequately answer the question of whether there are clinically relevant safety and/or efficacy differences from a reference active substance. Similarly, a package of data may be sufficient to show clinically and statistically significant differences, but may not be sufficient or appropriate to justify an approval.
- For the purposes of designation as a NAS only, the default position is that an enantiomer is not different from the racemate, unless proven otherwise. For the purpose of licensing decisions, there is no default position and the applicant should justify its position based upon the data provided.
- Direct comparison between the racemate reference active substance and the enantiomer is required to demonstrate the differences claimed and to justify designation as a NAS. Indirect, non-comparative evidence would not be suitable.

2.2. Type of evidence required to show differences

The legislation refers to differences in safety and/or efficacy being required to justify an isomer (enantiomer) being a NAS. This should be interpreted as clinically relevant human safety and/or efficacy differences. It is therefore anticipated that head-to-head clinical studies would be required to demonstrate clinically relevant differences in safety and/or efficacy. In addition the package of data may include pharmacological studies, animal models of disease, and toxicological studies (if safety differences are anticipated), where these are relevant to confirming the clinically relevant human difference, or have been conducted as part of the development programme to allow the clinical trial programme to commence.

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

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

- Significant changes to the dosing frequency (e.g. bd to od) mandated by the different properties of the enantiomer, if this is deemed to be clinically significant;
- Meaningful changes to the overall efficacy (e.g. clinically and statistically significant difference in the primary endpoint);
- Meaningful and clinically relevant changes that result in differences to contraindications, warnings or clinically significant adverse reactions;
- Meaningful and clinically relevant changes that affect significantly drug:drug interactions such that the population able to take the drug is significantly different;

- Meaningful and clinically relevant changes that allow the product to be used in a wider patient population or previously excluded sub-groups.

Evidence unlikely to be sufficient:

- Changes to pharmacokinetics alone (that do not alter elements above);
- Preclinical differences without clinical confirmation (with the possible exception of differences in reproductive toxicity or carcinogenicity);
- Extrapolation between studies: a direct head-to-head comparison is needed in a sufficiently powered study to show a clinically and statistically significant difference.

2.4. Ensuring robust designations are made

It is critical that designation of a substance as a NAS compared to an existing reference active substance are robust and agreed at a European level. It is important that the status of a medicinal product is appropriately determined at the time of first approval, and explicitly concluded in the published Assessment Report. It is therefore proposed that such designations are agreed at either the Committee for Medicinal Products for Human Use (CHMP) (for products handled via the centralised procedure) or the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh) (for products handled through national, mutual recognition or decentralised procedures).

2.5. Significance of filing route

It is the properties of the product, not the filing route that determine whether an enantiomer is deemed to be a NAS or not compared to a racemic reference active substance. Filing under Article 8(3)(i) of Directive 2001/83, as amended, does not automatically confer a NAS status, nor does filing through the centralised route. Agreement on designation as a NAS can only be made after a detailed assessment of the application. Where significant differences with regard to safety and/or efficacy are found and a NAS status for the enantiomer is confirmed, the 6/10 year period or the 8+2+1 period must be observed before an Article 10(1) generic application or 10(3) hybrid application may be made using the enantiomer as the reference product.

3. Conclusion

For newly assessed applications, the Rapporteur/Reference Member State/National Competent Authority should recommend whether or not the enantiomer is to be considered as a NAS in relation to a racemic reference active substance, and agree the recommendation with CHMP/CMDh prior to the issue being concluded. The assessment proposal will be agreed upon and published in the Assessment Report. This recommendation will be then followed for future generic/hybrid applications.

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 authorization - Chapter 1 marketing authorisation