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# E-ALERT | Food & Drug

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## NEW ACTIVE SUBSTANCE STATUS FOR NEW MEDICINES

Obtaining "new active substance" status for new medicines can be significant to innovative companies because it may determine whether their product benefits from data exclusivity.

Since the end of 2011, the European Medicines Agency assesses, as a rule, whether innovative products qualify as "new active substances". This note aims at shedding some light on the meaning, implications and uncertainties of this concept for medicinal products in the EU.

### 1. ACCESS TO CENTRALISED PROCEDURE *VERSUS* DATA EXCLUSIVITY

New active substance (NAS) status is relevant for two reasons.

First, it is a ground for access to the centralised procedure. Regulation 726/2004 provides:

- mandatory access in case a "medicinal product contains a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community" and is indicated for the treatment of certain diseases (Article 3(1) and Annex, section 3); and
- optional access for other new active substances (Article 3(2)(a)).

The test here is historical, namely whether the active substance was approved in the EU or EEA prior to 20 November 2005. In this context, a substance remains new even if it ultimately becomes genericised.

Second, the NAS status is relevant for data exclusivity purposes:

- If a substance qualifies as a new active substance, it benefits from a full period of data and marketing exclusivity (8 plus 2 years, potentially plus 1 year) under article 10 of Directive 2001/83.
- If it does not, it is considered -- unless developed by an independent company -- to fall under the "global marketing authorisation" of the earlier approved substance and will not benefit from a new period of exclusivity.[1]

Both notions are conceptually linked but a filing under the new active substance ground for access to the centralised procedure will not automatically lead to a finding of "new active substance status" for the purpose of data exclusivity. This e-alert focuses on this second meaning.

### 2. DEFINITION OF "NEW ACTIVE SUBSTANCE"

"New active substance" is not defined in the pharmaceutical legislation but in the Notice to Applicants:[2]

[1] For centrally approved products, this is being challenged before the EU courts (*Novartis Europharm v. Commission*, cases T-472/12 and T-67/13).

"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 significantly in properties with regard to safety and efficacy from that chemical substance previously authorised (...)".

In line with the above, the definition of a "generic medicinal product" contains the following presumption rule (the "new active substance presumption rule" or "presumption rule"):

> **"The different salts, esters, ethers, isomers, mixtures 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."**
>
> **(Article 10(2)(b) of Directive 2001/83)**

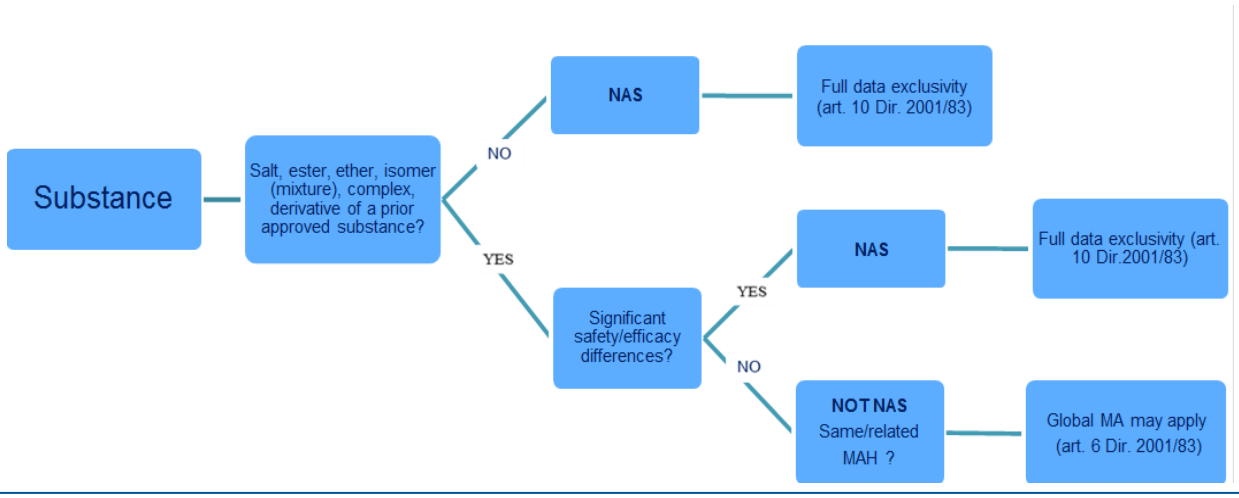
This rule, whose aim is to prevent simple modifications to existing products from benefiting of an additional full period of data exclusivity, has two components:

- It first defines the scope of application of the presumption, namely "salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives" of an existing active substance.
- It then contains a presumption that these substances will be considered to be the same active substance as the existing active substance, unless "they differ significantly in properties with regard to safety and/or efficacy."

Both parts of the test involve significant uncertainties. This makes it very difficult for companies to anticipate whether their substance will benefit from the new active substance status, and hence, from data exclusivity.

This new active substance and data exclusivity scheme can be illustrated as follows:

Table 1
New active substance and data exclusivity:




[2] Notice to Applicants, Volume 2a, Chapter 1, Annex I.

## 3. SCOPE OF THE SAME ACTIVE SUBSTANCE PRESUMPTION RULE

As a first step, it must be determined whether the substance is a "different salt, ester, ether, isomer, mixture of isomers, complex or derivative of an active substance." This is where the true difficulties begin:

- There is little guidance on the interpretation of those terms. While the meaning of salt, ester, ether and isomer is fairly circumscribed, this is not true for "complex" or "derivative". If interpreted broadly, these terms may cover almost all compounds somewhat composed of, or that can potentially be derived from another molecule.
- Determining what part of a compound is the "active substance" may also be tricky for complex molecules. This is even more difficult as the definition of active substance itself endorses the possibility that it is composed of a mixture of substances (article 1(3a) of Directive 2001/83).

## 4. REBUTTING THE SAME ACTIVE SUBSTANCE PRESUMPTION

Salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an earlier substance are thus presumed to be the same substances for data exclusivity purpose. This is unless "they differ significantly in properties with regard to safety and/or efficacy."

The EMA has recently released a Reflection Paper on this issue.[3] The preferred way for rebutting the presumption rule is through head-to-head comparison between the "reference active substance" and its variant (*e.g.,* a complex or derivative), demonstrating clinically relevant human safety or efficacy differences. Indirect, non-comparative evidence may be acceptable when scientifically justified but such data may be less compelling. Non-clinical data such as pre-clinical data, pharmacologic or pharmacodynamic studies, animal models of disease, microbiology studies and toxicological studies (if safety differences are anticipated) or other data may also be provided.

Reflection papers merely reflect the current status of discussions on a specific topic. They are not legally binding, nor are they meant to provide scientific or regulatory guidance.[4]

[3] 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, 18 October 2012, EMA/651649/2010.
[4] Procedure for European Union Guidelines and Related Documents withint the Pharmaceutical Legislative Framework, EMEA/P/24143/2004 Rev. 1, 18 March 2009.

**Table 2**

**Evidence likely to be sufficient to demonstrate a significant difference in safety or efficacy and justify a new active substance status according to the Reflection Paper:**

- Significant changes to the dosing frequency (*e.g.* bd to od);
- New route of administration mandated by significant differences in safety/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 resulting in differences to contraindications, warnings or clinically significant adverse reactions;
- Clinically relevant changes affecting significantly drug/drug interactions (*e.g.* significant change in the population able to take the drug);
- Clinically relevant changes allowing the product to be used in a wider patient population within the current indication or previously excluded sub-groups;
- Compelling preclinical data where it is not feasible to conduct head to head clinical studies (*e.g.* in case of differences in reproductive toxicity or carcinogenicity, the reference active substance is not authorised for the proposed indication).

The preference for head-to-head clinical studies raises several issues:

- This is extremely burdensome, in particular since such comparative studies are not a legal requirement for marketing authorisation.
- This is problematic for companies submitting applications now (or recently) as this requirement was not laid down in guidelines at the time of development of their product, so direct comparative data may not be readily available.
- This requirement is particularly inadequate for substances aimed for different populations or different therapeutic indications than the "reference" product. Although the EMA acknowledges that head-to-head trials may not be feasible in these cases, companies may struggle submitting "compelling preclinical data" demonstrating significant safety/efficacy differences between such molecules.

**Table 3**

**Evidence unlikely to be sufficient to demonstrate a significant difference in safety or efficacy and to justify a new active substance status according to the Reflection Paper:**

- Changes to pharmacokinetics alone;
- Preclinical differences that are inconclusive or unlikely to result in significant changes in clinical efficacy/safety;
- Extrapolation between studies (*i.e.* the claim for significant difference in efficacy is based on different studies for the reference active substance and the new form);
- Widening of the patient population to groups not previously studied for the reference active substance, if not substantiated with other robust data.

## 5. OTHER UNCERTAINTIES AND DIFFICULTIES

### Full dossier and new indication

According to the EMA Reflection Paper, the submission of a full application dossier does not imply NAS status. For the EMA, the NAS determination must be based on the properties of the substance. This must be kept in mind in particular when deciding to invest in molecules that show some similarity to already approved products of the same (or a related) company, but for a different therapeutic indication.

While a new indication may not automatically lead to the granting of the new active substance status, it can be a ground for benefiting from an additional year of data exclusivity (article 10(1), *in fine* of Directive 2001/83). In such case, a strategic choice needs to be made at an early stage as a request for an extra year of data exclusivity (for a known substance) is not compatible with a claim of new active substance.

### Standard for assessment

The EMA has been assessing the new active substance status of innovative medicines for about two years. So far, very few products have been denied such status (when claimed by the applicant). However, discussions on this issue are becoming more frequent. Public assessment reports typically contain very little information in that respect, making it difficult for companies to understand the standards applied by the EMA and to defend adequately the status of their product in case of doubt.

### Legal remedies

A finding by the EMA and the Commission that a product does not qualify as a new active substance is difficult to challenge. To bring an action for annulment before the Court of Justice, the product should normally be approved.[5] But as soon as the product is approved, generic filings are in principle permissible. If a company decides to withdraw its application to avoid that risk, it will also be more difficult to challenge the new active substance status finding before the EU courts.

[5] *Sepracor Pharmaceuticals v. Commission*, cases T-275/09 and C-477/11.

## 6. CONCLUSION

Many difficulties and uncertainties come into play when determining whether a substance is new or not. And these highlighted above are just illustrative. There are others, such as the legal value of the determination by the EMA, the notion of same marketing authorisation holder, the exact scope of the global marketing authorisation rule, the unclear link with similarity assessments under related legislation…

While technical and abstract, the new active substance question reveals its full range when a product is suspected by the EMA to be similar to another product of a company's portfolio. And this may well turn into a death sentence for the marketing authorisation. In the case of "Lunivia", Sepracor preferred withdrawing its marketing authorisation application than launching a product with no data exclusivity.

It is thus essential for a company to identify at an early stage potential issues pertaining to the new active substance status. This is done by identifying similar substances that have been approved in the EU (especially by the company itself or by a related company) and by applying the test described above. This strategy will enable the company to make conscious development decisions for new molecules, and, if need be, to timely prepare a robust file supporting a new active substance claim (*e.g.* through comparative studies or analysis).

So, is that product your company is developing a new active substance…?

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If you have any questions concerning the material discussed in this client alert, please contact the following members of our food & drug practice group:


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