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Concept of ‘Similar Medicinal Product’ in the context of the orphan legislation: adaptation to technical progress.

The UK supports the Commission proposal to review Regulation (EC) No 847/2000 and the opportunity to comment is welcomed.

The principal concern in the interpretation of the concept of ‘similar medicinal product’ is the anomaly with the considerations that are taken into account in the orphan designation. Specifically, when the orphan designation is based on benefit deriving from a different pharmaceutical form of an existing active substance as compared to products currently marketed. In these cases, the concept of ‘similar medicinal product’ is applied to all subsequent applications containing that active substance and claiming the same (now orphan) indication, irrespective of the nature of the pharmaceutical form.

Therefore, the UK considers it is helpful in some circumstances (for example for existing active substances) to define similar medicinal product with the additional reference to the specific pharmaceutical form. The inclusion of pharmaceutical form would reward the innovation of developing a new dosage form, but without obstruction of the authorisation of other forms of the same (existing) active substance.

The issue of consistency of approved indications for subsequent generic applications to orphan designated medicines after expiry of market exclusivity also requires consideration. In cases where indications overlap between different orphan medicinal products (e.g. Glivec & Tasigna), the more recently approved similar product (e.g. Tasigna) can effectively block inclusion of indications for subsequent generic marketing authorisations (e.g. generics for Glivec). This can result in different indications approved for the generic as compared with the reference medicinal product, undermining the principle of generic substitution. A solution to this interpretation should be considered.

The following specific amendments are proposed:

Lines 30-31

The sentence “*The principal molecular structural features are the relevant structural components of an active substance.*” is tautological and therefore unclear and unhelpful in interpretation of the intended message.

Lines 36-37

“...an active substance that differs from the original active substance only with respect to minor changes in the molecular structure, such as a structural analogue would be considered similar”

Given the difficulty in defining the threshold for non-similarity on structural comparison, it is recommended to highlight the need to consider both structural and functional elements (mechanism of action), when reaching a decision on similarity. For example, adrenaline and noradrenaline; liothyronine and levothyroxine; hydrocortisone and cortisone, respectively share similar structures but have different mechanisms of action.

Lines 71 to 73 (proposed changes in red font):

69 - If the difference in structure between them is due to post-translational
70 events (such as different glycosylation patterns) should be normally
71 considered similar. ~~However, the addition of an extensive glycan structure~~
72 ~~to the active moiety~~ **However, change to a post-translational modification**
of the active moiety significantly affecting functionality
(for example improving the binding capacity of the
73 substance) may result in a non-similar substance.

Rationale: The definition of extensive is subjective and less extensive modification to the glycan structure can impact binding capacity and result in a non-similar substance.

Lines 82-86

There is an apparent contradiction between lines 82-83 and lines 84-85 (as highlighted below):

82 - Monoclonal antibodies **binding to the same target epitope would normally**
83 **be considered similar**. However, two monoclonal antibody conjugates or
84 fusion proteins would be determined to be **non-similar if either the CDR**
85 **sequences of the antibody** or the additional structural element of the
86 conjugated monoclonal antibody were different.

Rationale: If monoclonal antibodies binding to the same target epitope are similar, why would monoclonal antibody conjugates (with the same conjugate) binding to the same target epitope/with the same CDR sequence be non-similar? It is also confusing to discuss binding to target epitopes and CDR sequences in adjoining sentences and it is recommended to use consistent terminology.

Suggested rewording:

82 - Monoclonal antibodies binding to the same target epitope would normally
83 be considered similar. However, two monoclonal antibody conjugates or
84 fusion proteins would be determined to be non-similar if ~~either the CDR~~
85 ~~sequences of the antibody~~ or the additional structural element of the
86 conjugated monoclonal antibody **or fusion protein** were **significantly** different.