Life Sciences & Healthcare Briefing: Special Edition

General Court of EU Judgement on Case T-483/22: Marketing Authorizations and Granting of Regulatory Advantages

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A. Context of the Case

1. The decision in Case T-483/22 Sanofi BV, formerly Genzyme Europe BV v European Commission, has provided useful reminders on the criteria for determination of an active substance as a new active substance (**NAS**) and on the granting of orphan status.
2. Sanofi BV sought partial annulment of the European Commission (the **Commission**)'s decision granting marketing authorisation for its product Nexviadyme – avalglucosidase alfa, a biological medicinal product for human use, without recognizing it as an NAS and without granting orphan medicinal product status.
3. Relying on the opinions of two committees of the European Medicines Agency (**EMA**)[1], the Commission granted authorization but declined both NAS status and orphan status. The Court upheld the decision, emphasizing the differences owed to EMA Committees on scientific matters and the applicant's evidential burdens for substantiating NAS and significant benefit.

B. Scope of Judicial Review over EMA Scientific Opinions

1. The Court reaffirmed that it will not substitute its own scientific assessment for those of CHMP or COMP.

[1] The CHMP and the COMP.

2. Judicial review is limited to verifying proper functioning, internal consistency, sufficiency of reasoning and the absence of manifest error, misuse of powers or an excess of discretion, and not to re-evaluating scientific merits.

C. New Active Substance: Stringent Application for Related Biologicals

1. The Court endorsed CHMP's verbatim approach to Annex I of the Notice to Applicants. An active substance falls within the definition of new under the first[2] indent, only if it is not related structurally to any authorised substance and does not expose patients to the same therapeutic component.
2. Where the substance is related and exposes patients to the same therapeutic component, the respective inquiry for marketing authorization shifts to the third indent of Annex I, which is whether differences in molecular structure, source material or manufacturing process result in a significant difference in safety and/or efficacy.
3. Applying this framework, the CHMP concluded that:
   a. avalglucosidase alfa is structurally related to the already authorized alglucosidase alfa (Myozyme), has the same amino acid sequence and exposes patients to the same therapeutic component;
   b. further to an analysis based on the third indent, the applicant had not provided sufficient evidence of significantly different safety or efficacy;
4. The Commission adopted this assessment, refusing NAS status and in this way precluding the follow-on product from benefiting from a regulatory data protection period of 8 years and a regulatory marketing protection period of 10 years[3]. The Court found no manifest error in this approach.
5. In summary, without sufficient evidence of a difference in safety and/or efficacy, redesigns or process modifications to a previously authorized product will not lead to an NAS status and will not secure the associated data and market protection periods.

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[2] Annex I to the Notice to Applicants, entitled 'Definition of a New Active Substance' provides that a new chemical, biological or radiopharmaceutical active substance includes, inter alia:
- a chemical, biological or radiopharmaceutical substance not previously authorised in a medicinal product for human use in the European Union ('the first indent of Annex I to the Notice to Applicants');
- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised in a medicinal product for human use in the European Union but differing significantly in properties with regard to safety and/or efficacy from that chemical substance previously authorised ('the second indent of Annex I to the Notice to Applicants');
- a biological substance previously authorised in a medicinal product for human use in the European Union, but differing significantly in properties with regard to safety and/or efficacy which is due to differences in one or a combination of the following: in molecular structure, nature of the source material or manufacturing process ('the third indent of Annex I to the Notice to Applicants').

[3] As provided for under Article 14(11) of Regulation No 726/2004.

D. Orphan Designation: Significant Benefit Must be Re-Established at Market Authorization Application

1. In its judgment, the Court underlines that significant benefit, defined as a clinically relevant advantage or a major contribution to patient care, must be demonstrated at the time of the marketing authorization (**MA**) in order to maintain orphan designation and benefit from the 10-year period market exclusivity[4].
2. COMP considered the evidence submitted at the time of granting the MA as insufficient to result in maintaining the orphan designation for Nexviadyme. This finding has been endorsed by the Commission, and the Court saw no error in this approach.
3. The takeaway is that applicants must substantiate using scientific data that the new biological brings a significant benefit over existing treatments that constitute the standard of care at the time of MA.

E. Key Practical Considerations

1. First, for sponsors of follow-on biologicals, relevance to an authorized substance and exposure to the same therapeutic component will channel the analysis to whether demonstrated differences in structure, source or process result in practice in significant safety and efficacy differences for the purposes of NAS classification. In the absence of compelling data, NAS will be refused.
2. Secondly, significant benefit proven at initial designation, must be re-demonstrated at MA application through comparative evidence supporting clinically relevant advantage or major contribution to care over approved therapies for the purposes of orphan maintenance.
3. These are useful reminders to be considered at the design stage of follow-on biologicals' development programs. These programs must be tailored to generate contemporary comparative evidence in order to meet both the NAS and orphan maintenance criteria.

[4] Under Article 8(1) of Regulation No 141/2000.



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