How should the "benefit-risk" concept of a medicinal product be interpreted?

Judgment of the General Court of the European Union of 15 May 2024 (T-416/22)

Background

This judgment concerns an appeal against the European Commission's Implementing Decision on marketing authorisations ("MAs") for medicinal products containing the active substance hydroxyethyl starch ("HES") indicated for the treatment of hypovolemia caused by sudden blood loss. All HES medicinal products had been authorised at national level by the Member States.

In order to properly comprehend the legal controversy resolved in this judgment, the following facts are relevant.

Since 2013, the products in question have been the subject of several evaluations regarding their benefit-risk balance, in particular due to an increased risk of renal dysfunction and mortality if administered to patients suffering from sepsis, burns or who are critically ill. The same year, the European Commission ordered the Member States to amend the MAs of HES medicinal products to include new contraindications and warnings and to reduce their posology.

In 2018, the Commission again ordered Member States to amend the marketing autorisations to HES medicinal products to include additional risk minimisation measures, as the measures initially adopted were not being respected in clinical practice. These additional measures included circumscribing the supply of the medicinal products in question to those healthcare professionals who had followed specific mandatory training, as well as including more visible warnings on the packaging.

In 2022, the Pharmacovigilance Risk Assessment Committee ("PRAC"), adopted an assessment report in which it concluded that (i) non-compliance with product information measures persisted; (ii) HES products continued to be used in populations in which they are contraindicated; and (iii) therefore presented an increased risk of serious harm, including mortality. The PRAC indicated that no additional measures could be identified that would sufficiently ensure the safe use of HES. The PRAC concluded that the benefit-risk balance of HESwas unfavorable and recommended discontinuing their MAs.

In view of this report and the conclusions also adopted by the CMDh, the Commission adopted the decision of 15 May ordering the Member States to suspend the MAs of HES medicinal products. However, the decision provided for an exception: Member States may, exceptionally, for a maximum period of eighteen months from the date of adoption of the decision, postpone the suspension.

Fresenius, holder of several MAs for HES medicinal products, appealed the decision before the General Court of the European Union (GC). As we have already mentioned, the GC rejects all the arguments put forward by Fresenius and dismisses the appeal in its entirety. However, we find it interesting to delve into the General Court's interpretation of the concept of "bene-

fit-risk” balance in relation to medicinal products for human use.

Should off-label use be taken into account in assessing the “benefit-risk” balance?

Fresenius claimed that the Commission had infringed Article 116 of Directive 2001/83/EC, which empowers the competent authorities to suspend, revoke or vary a marketing authorisation when it is considered, inter alia, that the risk-benefit balance is not favourable. In this regard, Fresenius considered that the suspension of a marketing authorisation was only possible if the product in question does not offer a favorable risk-benefit balance when used in accordance with its SmPC. According to Fresenius, the risks arising from off-label use should not influence the decision to suspend a MA.

The GC analyses how the concept of “benefit-risk” balance should be interpreted according to the wording, context and objective pursued in Directive 2001/83/EC and concludes that the risks related to the off-label use of the medicinal product can be taken into account in the benefit-risk assessment.

On literal interpretation

The GC notes that Directive 2001/83/EC defines the risk-benefit balance as “the assessment of the positive therapeutic effects of the medicinal product in relation to any risks related to the quality, safety and efficacy of the medicinal product for the health of the patient or for public health”. On the basis of this wording, the GC concludes that this concept is sufficiently broad to allow the risks related to the off-label use of a medicinal product to be taken into account.

On contextual interpretation

The GC focuses on the information obligations of all marketing authorisation as set out in Article 23 of Directive 2001/83/EC. Among these, it is expressly provided for the obligation for the marketing authorisation holder to communicate to the national competent authority the “data on the use of the medicinal product when such use does not comply with the terms of the [marketing authorisation]”. This reporting obligation, the GC points out, would be meaningless if the competent authority could not take these data into account and draw consequences from them.

In addition, the GC sets out the purpose and scope of the data to be collected from the pharmacovigilance system regulated in Article 101 of Directive 2001/83/EC. This provisionexpressly states that the information to be collected in the pharmacovigilance system shall relate to adverse reactions caused by the use of a medicinal product in accordance with the terms of the marketing authorisation “and by uses outside such terms”. Relying on this idea, the GC concludes that Directive 2001/83/EC does not contain any provision indicating that the risks of off-label use of a medicinal product should be taken into account for the purposes of the pharmacovigilance system, but not for the purposes of deciding on the revocation, suspension or modification of a marketing authorisation.

Lastly, the GC notes that the fact that Article 116 of Directive 2001/83 does not contain any reference to “normal conditions” of use corroborates the Commission’s interpretation that the concept of “risks related to the use of the medicinal product” also covers risks related to its use outside its marketing authorisation.

On teleological interpretation

According to the GC, Article 116 of Directive 2001/83 must be interpreted in accordance with its ultimate objective: the safeguarding of public health. To this end, the competent authorities must be able to take into account information on all risks to public health posed by a medicinal product, including those related to its off-label use.

In this regard, the GC reinforces its interpretation with the preparatory works of Directive 2010/84, which amended, among others, Article 116 of Directive 2001/83. It follows from them that the Commission deleted the concept “normal conditions of use” because “it is not defined and could be interpreted as restricting regulatory measures in case of a serious public health issue related to off -label use”.

Conclusion

In view of the foregoing, the GC concludes that it follows from the literal, contextual and teleological interpretation of Article 116 of Directive 2001/83 that the Commission acted correctly in assessing the benefit-risk balance of medicinal products containing HES as an active substance, taking into account the risks involved in their off-label use.

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