Conditional marketing authorisation: easier to grant than to revoke

● Progesterone is ineffective at preventing preterm delivery, but proved difficult to withdraw from the market. It is not the only example of this phenomenon.

Many marketing authorisations are granted despite inadequate evaluation, with certain conditions attached, such as a requirement to conduct clinical trials after the product's market introduction: they are conditional marketing authorisations. When the trials demanded show that the product has an unfavourable harm-benefit balance, its marketing authorisation is sometimes difficult to revoke.

Intramuscular *hydroxyprogesterone* (Makena°) was authorised by the US Food and Drug Administration (FDA) in 2011 to prevent recurrence of preterm birth, on the basis of a trial showing it to be more effective than placebo at reducing the risk of birth before 37 weeks of gestation (1). Marketing authorisation was granted on condition that the company produced results showing efficacy in reducing neonatal morbidity and mortality from complications of preterm birth. The trial, conducted for this purpose and completed in 2018, did not demonstrate the product's efficacy in improving these outcomes (1).

Clinical trial data from as far back as 2016 had shown that *progesterone* has no efficacy in this indication (2,3). Vaginal *progesterone* was "delisted" in France in 2017, i.e. removed from the list of reimbursable drugs and from the list of drugs approved for use in hospitals, as a means of limiting its use (4).

In 2019, an FDA advisory committee concluded that the conditions attached to this marketing authorisation had not been met, but the pharmaceutical company requested a hearing to contest its withdrawal (5). In September 2022, the FDA's internal evaluators again recommended revoking the marketing authorisation for Makena°, due to lack of efficacy and its adverse effects for the mother (in particular deep vein thrombosis) (1).

The pharmaceutical company's request to retain approval for Makena° for use in certain women was echoed by a number of doctors and members of the public, in particular by certain African American groups among whom preterm birth is more common than in the general population (6). In April 2023, the FDA's Commissioner and Chief Scientist finally decided to withdraw approval for Makena° (7).

This situation is reminiscent of the fiercely contested decision to withdraw the US conditional marketing authorisation for *bevacizumab* (Avastin°) in breast cancer, as well as the opposition of certain associations of doctors and patients to France's decision to delist drugs authorised for Alzheimer's disease (6,8,9).

The FDA considered that if the results of the clinical trial of intramuscular *hydroxyprogesterone* published in 2019 had been available in 2011, it would not have granted conditional approval. It is an excellent reason not to grant marketing authorisations prematurely, especially given how difficult they are to subsequently revoke.

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