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Influence on regulatory decisions for drugs with limited evidence

Conflicts of interest and political and emotional pressures are key challenges

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Regulatory agencies face growing pressure to approve drugs despite major safety and efficacy concerns. Over decades, this pressure has led to the creation of faster and more flexible regulatory pathways that increasingly rely on surrogate endpoints and limited clinical evidence to speed up market access and commercial returns.[1,2] Even newer policy innovations continue to prioritise faster access over stronger clinical evidence. For instance, the recent introduction of the Medicines and Healthcare Products Regulatory Agency-National Institute for Health and Care Excellence (MHRA-NICE) aligned pathway for regulatory and reimbursement assessments in the UK aims to enable simultaneous decision making and to speed commercial access 3-6 months earlier.[3]

For diseases with high unmet need, external pressures can influence how evidentiary standards are interpreted. Stronger transparency, clearer communication, and stricter safeguards against conflicts of interest are needed to protect patients and preserve public trust in regulatory decision making.

Lack of efficacy in Alzheimer's disease drug trials

Alzheimer's disease is one example of where approval was granted for drugs despite limited evidence. In 2021, the US Food and Drug Administration (FDA) approved aducanumab for Alzheimer's disease from two pivotal studies, even though there was conflicting evidence of efficacy. Both studies were initially terminated for futility, but it was later announced that one trial (Emerge) found a statistically significant effect in patients receiving the high dose.[4] Previous trials had failed to show clinical benefits from amyloid immunotherapy, and the relation between amyloid β clearance, reduced tau deposits, and meaningful cognitive improvement remain uncertain.[5]

Approval was granted despite the advisory committee's overwhelmingly negative opinion, leading to the resignation of three members in protest.[6-8] In contrast, the European Medicines Agency (EMA) rejected aducanumab, based on an overall negative benefit-risk balance as the submission relied largely on post-hoc analyses, inconsistent results, and an effect size below the minimal clinically important threshold.[9]

Lecanemab and donanemab faced similar challenges - though intended to treat Alzheimer's disease, they were initially rejected by the EMA but later authorised for restricted populations. For lecanemab, the EMA's Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion, but almost half of its members then publicly voiced their disagreement, raising concerns regarding the reliance on a single study, limited clinical relevance, and substantial safety risks.[10] Market authorisation was nevertheless granted,[11] a decision which may have also been influenced by unsolicited reactions from patients, patient organisations, and self-appointed expert groups.[12] When uncertainty of evidence is high, and when disease burden is substantial, decision making is more likely to be influenced by external expectations from commercial interests, patients, and families than robust clinical evidence.

Similar challenges in Duchenne muscular dystrophy

Another notable case of regulatory approval granted under strong patient and political pressure is eteplirsen for Duchenne muscular dystrophy.[13] Initially, the FDA's Division of Neurology Products and Office of Drug Evaluation recommended against approval. However, senior FDA leadership ultimately granted accelerated approval based on evidence on the surrogate endpoint of dystrophin levels, which the FDA committee initially rejected as a suitable endpoint.[13-16] By contrast, the EMA denied market authorisation, concluding that eteplirsen's efficacy was unproved and that its safety profile was insufficiently characterised.[17]

After approving eteplirsen, the FDA granted accelerated approvals to two additional exon skipping therapies for muscular dystrophy, golodirsen [18] and casimersen,[19] despite similar concerns remaining unresolved. Although the EMA did not authorise these drugs, it had already conditionally approved another treatment in 2014, ataluren, despite substantial objections from numerous CHMP members.[20] Ataluren's single pivotal study failed to show efficacy on both the primary and secondary endpoints, relying solely on post-hoc and subgroup analyses.

Ten years later, after re-evaluating the evidence, the EMA decided not to renew ataluren's marketing authorisation.[21] Although the original approval was conditional, requiring subsequent reassessment, the delay before revocation shows how such accelerated pathways can lead to years of funding costly, ineffective therapies, ultimately harming overall health outcomes.

These regulatory divergences may partly reflect the underlying uncertainty in the evidence, but it is also possible that external pressure affects FDA and EMA decision making.

Cultural and institutional reform is needed

The current rhetoric is that regulators are too slow, that patients cannot wait, and that people should

decide for themselves what risks to take.[22] Patient desperation is often used as a moral justification to loosen scientific evidentiary standards.[13] The most important question is how to balance the tension between hope and evidence, between desperation and scientific discipline.

Addressing these issues demands fundamental changes. A critical first step is to ensure that all advisers and experts involved in regulatory assessment and decision making are free from conflicts of interest. The EMA was recently required to revise its rules on managing competing interests after the EU Court of Justice annulled a CHMP decision because of involvement of experts with declared commercial interests.[23]

Another important step is to strengthen governance safeguards to ensure that regulatory decisions remain grounded in transparent scientific reasoning. The opinions of expert reviewers and advisory committees, together with remaining uncertainties, should be clearly disclosed alongside the rationale for final decisions. However, such disclosure is of limited value if the nature and extent of remaining uncertainties are not communicated in clear and accessible language. Well informed patients may be better positioned to advocate for more robust studies, rather than pushing for the premature adoption of drugs with questionable evidence. Protecting scientific integrity requires keeping commercial and political pressures out of regulatory decisions.

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