REGULATORY CHALLENGES AND INSIGHTS FROM FDA IN 2025; POTENTIAL IMPLICATIONS OF THE PLAUSIBLE MECHANISM PATHWAY AND SUBSEQUENT HTAS

HPR146

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INTRODUCTION

- Regulatory and health technology assessment (HTA) processes require a different focus; the disconnect between these processes, and the different evidence required, can be a significant barrier to timely patient access.
- In particular, drugs for orphan diseases have historically faced regulatory and HTA challenges due to small patient populations, limited natural-history data, reliance on single-arm trials, and high acquisition costs. Thus, it is harder to demonstrate substantial evidence of effectiveness, ultimately delaying patient access where there is an unmet need.
- In recent years, regulatory authorities have been reassessing how therapies for rare diseases should be evaluated:
  - MHRA's Innovative Licensing and Access Pathway (ILAP) is an initiative which aims to accelerate the time to patient care for transformative new medicines, and claims to be *"the only end-to-end access pathway in the world where the developer can work collaboratively with the national health system, the regulator and HTA bodies."*[1]
  - As of April 2026, the MHRA-NICE Aligned Pathway aims to get new medicines to patients 3 – 6 months sooner by bringing NICE decisions forward to align with MHRA i.e. delivery of regulatory and HTA decisions at the same time.[2]
  - EMA's Accelerated Assessment reduces the timeframe to review a marketing authorization application or products of major public health interest or therapeutic innovation.[3] Similarly, the FDA's Accelerated Approval program allows for earlier approval of drugs that treat serious conditions and fill an unmet medical need based on a surrogate endpoint.[4]
  - In February 2026, the FDA launched the Plausible Mechanism Framework for targeted individualized therapies (that target a specific genetic, cellular or molecular abnormality) to support the generation of substantial evidence of effectiveness and safety when randomized controlled trials are not feasible due to small patient populations.[5]

Research objective

The purpose of this analysis was to explore reasons given by FDA for issuing Complete Response Letters (CRLs – i.e. not approved in its current form), and discuss the impact of innovative methods to allow greater flexibility in regulatory evidence requirements, including potential implications for subsequent HTAs.

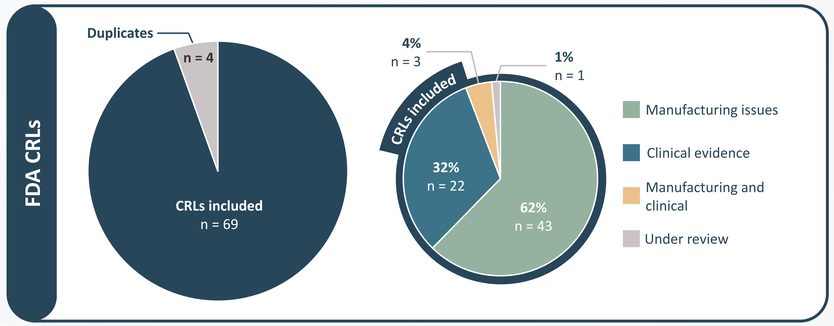
METHODS

- The CRL section of the FDA website was searched for all CRLs issued in 2025 to present day (April 2026).[6]
- Targeted grey literature searches were also utilised to gather additional information.
- Indication, orphan status, whether the drug was an ATMP, and key drivers of the FDA decision were recorded.

RESULTS

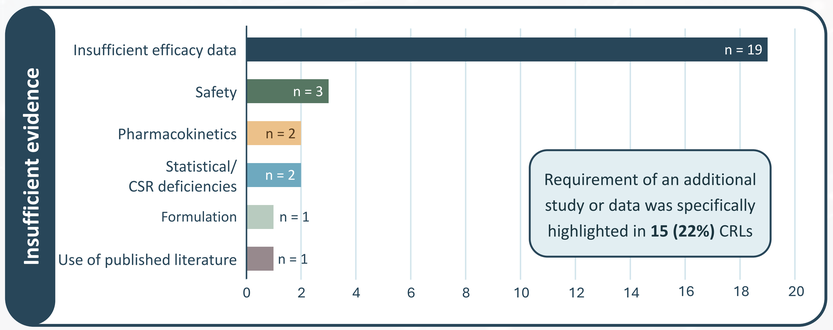
- 73 CRLs were issued by FDA between 1 January 2025 and 15 April 2026. 4 CRLs were removed from the analysis due to being the same BLA/NDA number i.e. only the most recent CRL was included, therefore 69 CRLs were included in this analysis (Figure 1).
- 15 (22%) were for orphan drugs and 6 (9%) were ATMPs.

Figure 1: number of CRLs issued by FDA since 2025 and key reasons for decision



- Figure 2 shows the reasons why the clinical data were not deemed sufficient in 25 CRLs to demonstrate evidence of effectiveness*.

Figure 2: reasons provided by FDA for insufficient clinical evidence*



- 12 of the 15 (80%) orphan drugs were due to clinical data not providing sufficient evidence of effectiveness.
- Of the 19 CRLs issued due to insufficient evidence of effectiveness*, reasons provided by the FDA included were: lack of robust clinical benefit (17), issues with study design e.g. single arm studies (7), issues with the analysis/plan (3), study population (3), appropriateness of endpoints (3).
- While a formal CRL was not issued by FDA, grey literature searches identified AMT-130, a treatment for Huntington's disease; the FDA does not agree with the company's plan of using phase I/II studies to support an application for AMT-130, and "strongly recommend conducting a prospective, randomized, double-blind sham surgery-controlled study".

CONCLUSION

- The data show that of the drugs not approved by FDA due to the submitted evidence (rather than manufacturing/compliance issues), the majority (76%) were due to insufficient evidence of effectiveness in the clinical dataset (Figure 2). This percentage rises to 80% when only considering orphan drugs.
- These recent FDA decisions highlight the extent to which flexibility in the evidence package for orphan diseases is required. Where significant changes to the clinical evidence are needed, sponsors and patient groups raise concerns that a generation of patients may go without access to a potentially life-saving therapy.
- The FDA's Plausible Mechanism Framework, alongside EMA and MHRA initiatives, represent an evolution in regulatory thinking for rare and high unmet need therapies, particularly in a landscape whereby individualized therapies for ultra rare diseases are likely to become more common.
- International experience, for example from the UK's ILAP, demonstrates that integrated approaches can reduce uncertainty and accelerate patient access. However, most of the therapies included in this analysis would likely not have benefited from the Plausible Mechanism Framework due to not meeting the criteria.[1]
- The recent case of AMT-130 for Huntington's disease also raises ethical questions around the FDA's recommendation to conduct a sham brain surgery control arm, and further highlights that flexibility may also need to be applied on a case-by-case basis particularly where there is a considerable unmet medical need.
- To realise its potential, regulatory policy intent must be matched by operational clarity, consistent application, and alignment with reimbursement systems.
- Indeed, without complementary flexibility at the reimbursement level, innovative medicines for rare disease may fall at the final hurdle; HTA bodies will still require robust comparative evidence, particularly in markets where cost-effectiveness estimates are a key driver of decision making.
- Increased regulatory flexibility, therefore, may lead to increased reliance on managed access agreements or conditional reimbursement while data are collected post-launch.

Abbreviations: ATMP, Advanced Therapy Medicinal Product; CRL, Complete Response Letter; EMA, European Medicines Agency; FDA, Food and Drug Administration; HTA, Health Technology Assessment; ILAP, Innovative Licensing and Access Pathway; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence.

Footnotes: *some CRLs were issued for multiple reasons, therefore the total is greater than 25

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