

PINK SHEET

Regulatory News & Insights

Navigating the Rare Disease Approval Landscape

Evidence, Flexibility, and the Path Forward
2026 Rare Disease Regulatory Webinar



Speakers



Derrick Gingery
US Executive Editor,
The Pink Sheet



Bridget Silverman
Managing Editor,
US Regulatory Analysis

Why This Moment Matters



Recent Approvals...

- **10 novel orphan product approvals** in 2026, accounting for 45% of novel approvals
 - Orphan products have **consistently** made up about half of novel approvals for a decade
- The 2026 class includes the **first FDA-approved therapies** for
 - Arginase 1 deficiency (Immedica's Loargys)
 - Neurologic MPS II (Denali's Avlayah)
 - Genetic hearing loss (Regeneron's Otarmeni)
 - Hepatitis D (Gilead's Hepcludex)



...But Rising Rejections

- **5 CRLs** for novel rare disease candidates in 2026
 - All the orphan CRLs call for new clinical evidence
- Rare disease rejections **spiked** to 14 CRLs in 2025, double the number in 2024
- **Neurology** is the most common therapeutic area for rare disease CRLs

FDA is not less flexible — it is applying flexibility in unpredictable ways.

Key Statistics: Rare Disease Drug Development

49%

of all FDA novel approvals carry orphan drug designation (2016–2026)

61/119

novel approvals in 2024–2025 were for orphan indications

18%

of 2026 novel approvals are neuroscience therapies (consistent with 16% historically)

7 of 10

CBER neuroscience approvals in the last decade occurred in 2023 or later

Session Roadmap

.....
APPROVAL SUCCESSES

.....
CAUTIONARY CASES

.....
CNS RARE DISEASE CRLS

.....
POLICY LANDSCAPE
.....

Case Study: Kresladi (marnetegrane autotemcel) for LAD-I

APPROVAL

At a Glance

Developer:

Rocket Pharmaceuticals

Disease:

LAD-I (≈450 cases ever reported)

Design:

Single-arm, 9 patients

Endpoint:

HSCT-free survival vs. natural history control

Approval:

Accelerated approval granted

What Persuaded FDA

- Objective biomarker (LFA-1 restoration) is less prone to bias than clinical measures
- Biological plausibility as confirmatory evidence: single-gene defect, well-understood pathway
- Unmet need: LAD-I is fatal; no alternative for patients without matched sibling donors
- Post-marketing requirements include long-term outcomes on ≥ 10 patients for 15 years

Key Takeaway: In settings with limited clinical outcome data, a well-characterized molecular pathway can carry significant evidentiary weight.

Case Study: Zycubo (copper histidinate) for Menkes Disease

APPROVAL

At a Glance

Developer:

Sentynl Therapeutics

Disease:

Menkes (1 in 50k–250k births)

Design:

Two open-label studies + external control

Endpoint:

Overall survival (hard endpoint)

Effect size:

78% reduction in risk of death

Approved Despite Serious Data Concerns

- FDA Form 483 issued (Official Action Indicated) for “significant data reliability concerns”
- Sensitivity analyses found consistent survival benefit across all assumptions
- Mechanistic biomarker data confirmed biological activity independent of contested clinical data
- FDA explicitly articulated a sliding scale: greater unmet need + robust benefit = more uncertainty tolerated

"The substantial and robust survival benefit observed allows greater uncertainties in the knowledge of safety." — FDA review

Cautionary Case: Bitopertin for EPP/XLP (Disc Medicine / Roche)

At a Glance

Disease:

Erythropoietic protoporphyria/X-linked protoporphyria (1 in 75,000 prevalence)

Design:

2 RCTs; accelerated approval sought

Surrogate:

40% reduction in blood protoporphyrin IX (PPIX)

Issue:

No correlation between PPIX and sunlight tolerance in trials

Outcome:

Complete Response Letter

Why the Surrogate Failed

- PPIX moved and FDA agreed drug **had an effect on** the surrogate
- But sunlight exposure/tolerance endpoints showed **no correlated change** in either trial
- Biological plausibility alone is **not sufficient** when trial data actively undermines correlation
- Modest 40% reduction: **smaller effects** require stronger demonstration of surrogate-to-outcome link
- **Path forward:** adequate and well-controlled trials with clinical endpoints

Lesson: *Biological plausibility is a starting point, not a finish line. Your own trial data must show the biomarker tracks with how patients feel and function.*

CNS Rare Diseases: Why Disproportionate CRL Rate?



Subjective Endpoints: Cognitive function, behavioral symptoms, and quality of life are variable, bias-prone, and hard to validate as surrogates.



Limited Natural History: Many rare CNS diseases lack robust natural history data.



Blood-Brain Barrier: Target engagement in CNS requires invasive sampling or proxy biomarkers that carry their own correlation uncertainty.



Patient Heterogeneity: Variable genotype, age of onset, and progression rate heterogeneity makes treatment effect estimates noisier.



CNS CRL: RGX-121 (clemidsogene lanparvovec) for MPS II — Regenxbio

The CRL identified three interlocking problems:

1

Patient Identification

Eligibility criteria did not adequately distinguish neuronopathic from attenuated MPS II. FDA cannot approve for a population that wasn't reliably enrolled.

2

External Control Comparability

Age differences and inconsistent cognitive impairment definitions undermined comparability between the 13 trial patients and external control

3

Unvalidated Biomarker

CSF HS D2S6 has never been used in a regulatory decision, lacks published literature support, and had no established threshold. Intra-patient variability from two sampling routes further undermined the within-patient control.



Bottom Line

- ❖ Each issue was individually addressable, but cumulatively decisive against approval of a 13-patient study
- ❖ Path forward likely requires a larger, more rigorously controlled trial with a prospectively validated biomarker and clearer eligibility criteria

CNS CRL: Troriluzole (Vyglxia) for Spinocerebellar Ataxia — Biohaven

What Biohaven Submitted

3-year real-world evidence study (Study 206-RWE) with statistically significant primary endpoint and 8 consecutive secondary endpoints

- External controls from two independent natural history databases (CRC-SCA, EUROSCA)
- ~15,000 US patients; no approved treatment options for spinocerebellar ataxia

FDA's Response

Effect was not “sufficiently large or robust” to overcome methodological limitations

- Post-hoc, unblinded, not prespecified analysis is vulnerable to unmeasured confounding

Key Trend: Fewer AdComs

Advisory committee review was planned, then cancelled by FDA — a notable departure from prior practice

- Advisory committee meetings dropped from 38 in 2024 to 14 in 2025 — a >70% decline that materially changed the review landscape

CNS CRL: Vatiquinone for Friedrich's Ataxia — PTC Therapeutics

A pivotal trial missed its primary endpoint, but firm sought approval anyway

Trial	MOVE-FA: RCT with mFARS as primary endpoint at 72 weeks — missed
Argument	Significant improvement on USS subscale; stronger mFARS benefit at 144 weeks; natural history + OLE comparisons; biomarker data
FDA on trial	USS finding was exploratory, not prespecified; clinical meaningfulness “uncertain”; small difference vulnerable to baseline confounding
FDA on NatHx	USS benefit in MOVE-FA “not independently substantiated” by OLE vs. natural history. (After 3 years, no USS benefit was observed in FDA’s assessment.)
FDA on biomarkers	Could contribute confirmatory evidence “in the setting of a positive adequate and well-controlled study”
Path forward	Prospective RCT in pediatric subjects with USS as primary endpoint suggest — But FDA later clarified in a December 2025 Type C meeting that a single-arm with natural history comparator may suffice.

Policy Landscape: Three Developments to Watch

UniQure / Huntington's Disease

The company said that FDA reversed its position pre-BLA filing and said that external control no longer sufficient for HD. The agency argued that two decades of consistent policy require RCT for subjective, heterogeneous endpoints. UniQure called it a “drastic change” and the public dispute escalated to Commissioner level.

Leucovorin for Cerebral Folate Transport Deficiency

Approved was based on FDA's own review of 28 published case reports. There were no clinical trials and was no formal development program. The available data did have a lot going for it, however: There was a known genetic defect, the product had a direct mechanism and boasted 70 years of safety data, while the case reports showed a 87% patient benefit rate. This is another instance of large effects and strong mechanism overcoming major evidence gaps.

The Haystack Petition

Coalition of 160+ rare disease groups, with former CDER Director Woodcock, petitioned FDA in April 2026 to codify a “framework for contextual scientific evaluation” that would flip the default from “RCT unless justified” to “evaluate study design against the specific disease context.” With PDUFA reauthorization approaching, this idea could find its way into legislative language.

5 Key Takeaways for Rare Disease Development



Effect size is the through-line. Large, unambiguous, mechanistically grounded effects unlock acceptance of single-arm studies, external controls, and biomarker surrogates



Invest in natural history early and deeply. It **underpins every viable alternative to RCTs** and its absence is frequently fatal to an **application**



Validate your biomarkers **before pivotal studies**. Biological plausibility is a starting point. Your own trial data must show the biomarker tracks **clinical outcomes**



Prespecification and rigor in RWE are non-negotiable. Post-hoc analyses face a burden of proof that **prospective designs** do not

Document FDA alignment carefully. What is understood at one stage does not always survive to the review — write it down.

Keep an Eye Out — Especially August & September 2026

At least 45 pending applications for rare/orphan diseases, including these first-ever therapy candidates with challenging endpoints

Nov. 17

Adrabetadex

Mandos

Niemann-Pick disease type C

ENDPOINT CHALLENGE: Endpoints measuring neurological function in infants are poorly standardized.

BTD

RPD

Aug. 23

Pariglasgene brecaparvovec

Ultragenyx

Glycogen Storage Disease Type Ia

ENDPOINT CHALLENGE: Primary endpoint, reduction in cornstarch intake, is a surrogate; FDA must accept it predicts long-term complications that continuous glucose management with cornstarch also fails to prevent.

RMAT

RPD

Sept. 22

Zilganersen

Ionis

Alexander disease

ENDPOINT CHALLENGE: Poorly characterized natural history; functional endpoints not disease-specific. Intrathecal bolus delivery every 12 weeks adds regulatory complexity.

BTD

RPD

Sept. 27

Relutrigine

Praxis Precision Medicines

SCN2A/SCN8A Developmental & Epileptic Encephalopathies

ENDPOINT CHALLENGE: Seizure frequency is measurable but developmental outcomes are slow-moving and hard to capture in trial timeframes.

BTD

RPD



Q&A

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