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This Week's Top Global Headlines

The Anatomy of an Approval

For a child with Alexander disease, it may begin with missed motor milestones, struggling to walk, seizures, muscle weakness, or progressive neurological decline. For families, the question is painfully practical…is there finally a treatment option, and is the evidence strong enough to support its use?

That is what makes FDA's approval of Zanvastro worth unpacking.

Zanvastro is the first FDA-approved treatment for Alexander disease and the first therapy designed to target the protein buildup that drives the disease. The approval was supported by a multicenter, randomized study in patients aged 2 years and older, plus an open-label sub study in children younger than 2, with FDA considering age-appropriate clinical measures, pharmacokinetic modelling, and safety data across the pediatric population. **More info here.**

This was not a straightforward approval built around one large trial, one uniform patient population, and one endpoint. Alexander disease is too rare and too variable for that kind of evidence model. Instead, FDA had to evaluate a more tailored evidence package: different clinical measures for different age groups, limited direct evidence in infants, pharmacokinetic modelling, and safety data across a vulnerable pediatric population.

This week's Anatomy of an Approval looks at how the evidence was rationalized and what the FDA decision teaches rare-disease developers about building a scientifically defensible case when conventional trials are not possible.

Deep Dive

Some approvals are important because they introduce a new product. Others are important because they show how regulators think when the usual evidence model does not fit.

Zanvastro falls into the second category. Alexander disease is ultra-rare, progressive, and clinically variable. It can affect infants, children, and adults differently. That creates a development problem from the outset: a conventional large, uniform trial with one clean endpoint across all patients is not realistic.

So, the regulatory review seeks to address the question: "Can the totality of evidence be rationalized in a way that supports the proposed indication?"

For Zanvastro, FDA evaluated a multicenter, randomized, controlled study in 49 patients aged 2 years and older, plus an open label sub study in four patients younger than 2. The evidence

package was not identical across age groups, because the disease does not present identically across age groups.

In patients aged 5 years and older with measurable walking difficulties at baseline, FDA considered walking speed at 61 weeks. In children aged 2 to 4 years, where walking speed is not a reliable measure of progression, FDA considered a broader motor-function assessment, including standing, walking, running, and jumping.

For infants under 2, direct clinical evidence was necessarily limited. FDA relied on pharmacokinetic modelling to show that expected drug levels would be similar to those in older children at the same dose, supported by safety data from the four younger patients and the broader pediatric safety dataset.

That is the most interesting part of the approval. This is where rare-disease evidence strategy becomes more than trial design. It becomes a debate about clinical logic, biological plausibility, measurement relevance, and the responsible use of limited data.

The evidence had to connect several things:

- the disease mechanism;
- the drug's intended biological effect;
- age-appropriate clinical outcomes;
- safety across a vulnerable population;
- pharmacokinetic modelling for the youngest patients;
- and the rationale for an indication spanning infancy through adulthood.

That is a sophisticated regulatory story.

It does not mean evidence standards were lowered. It means the evidence standard had to be applied differently because the disease, population, and feasible study design demanded it.

For rare-disease developers, this is the key lesson: flexibility is possible, but it has to be earned.

Regulators may be willing to consider smaller studies, age-specific endpoints, modelling, limited direct evidence, and supportive safety data. But those elements need to form a coherent evidentiary bridge. Each piece must explain why it is relevant, what uncertainty remains, and why the overall package supports the decision being requested.

The Zanvastro approval is therefore not just a rare-disease milestone. It is a useful case study in evidence rationalization. It shows that when conventional development is not possible, the burden shifts to scientific explanation: why this endpoint, why this model, why this population, why this extrapolation, and why this totality of evidence is sufficient for the proposed use.

ECNE Insight

Rare-disease evidence strategy should begin with: "What decision does the evidence need to support, and how can each piece of evidence be made interpretable?"

At ECNE Research, we see this as one of the most important disciplines in rare-disease and complex-product development. When patient numbers are small, disease expression varies, and conventional endpoints do not fit every age group or clinical presentation, sponsors need more than data. They need a defensible evidence rationale.

That means mapping the logic early:

- what is known about the disease mechanism;
- which outcomes are meaningful for each patient group;
- where modelling or extrapolation may be appropriate;
- what safety evidence is needed for vulnerable populations;
- and how remaining uncertainty will be explained and managed.

The strongest rare-disease programs are those that build a clear, scientifically grounded bridge between what can realistically be studied and what regulators, clinicians, patients, and families need to know.

The real lesson from Zanvastro is not that rare-disease evidence can be smaller. It is that rare-disease evidence has to be better rationalized.

On Our Radar

- **USA | 9 September 2026 — FDA town hall on biocompatibility risk assessment:** FDA will host a town hall for industry on updates to ISO 10993-1:2025 and risk-based approaches for evaluating biocompatibility endpoints for medical devices. The FDA will share risk assessment approaches for evaluating biocompatibility endpoints for medical devices, with specific examples for evaluating material-mediated pyrogenicity and systemic endpoints. **More info here.**