How did an FDA ‘Breakthrough’, NMPA ‘Innovative’ Intracranial Stent, Designed, Patented, and Made in China, Get Rejected… by China Regulators?

The COMETIU Case Study – October 2025

I. Abstract

This case study, written by VVR Medical based on public sources and in-house expert analyses, deep-dives into the divergent regulatory outcomes for the COMETIU intracranial drug-eluting stent. The device, developed by the Chinese firm Sinomed, presents a significant paradox. In August 2025, the U.S. Food and Drug Administration (FDA) granted it a Breakthrough Device Designation. Its application under the European Union's stringent Medical Devices Regulation (EU MDR) is progressing, having passed quality system audit and entered final technical review. Yet, on October 28, 2025, China's National Medical Products Administration (NMPA) rejected its domestic registration application. This occurred even after the NMPA had accepted the device into its own premier "Innovative Medical Device Special Review Procedure".

The discrepancy appears contradictory, insofar as it suggests a fundamental disagreement on the device's merit among three of the world's most sophisticated regulatory bodies. Our analysis, however, concludes that said divergence is not a conflict over the device's ultimate potential. Instead, it is a logical consequence of different regulatory frameworks being applied at distinct stages of the product lifecycle.

The NMPA rendered a final judgment on a request for full marketing approval, which was supported solely by single-arm clinical trial data. In contrast, the FDA and EU regulators assessed similar data as sufficient grounds to grant or advance an expedited pathway. These pathways are intended to facilitate the generation of more robust evidence required for eventual market approval.

The COMETIU case, therefore, is not a story of a failed device. It is a powerful demonstration of a mature Chinese regulatory system, that has been elevating its evidentiary standards for high-risk devices to align with global best practices.

II. The Technology and the Indication

The COMETIU Stent System at a Glance

The COMETIU is a self-expanding, drug-eluting stent system engineered for the endovascular treatment of intracranial atherosclerotic stenosis (ICAS). Its design reflects a modern approach to the unique challenges of neurovascular intervention.

- **Stent Platform:** The stent is constructed from a medical-grade nitinol (nickel-titanium) alloy. This material's super-elasticity and shape memory properties are critical for navigating and conforming to the tortuous vasculature of the brain.
- **Mechanism of Action:** The stent's surface is coated with a biodegradable polymer, polylactic acid-glycolic acid (PLGA). This polymer serves as a matrix for the antiproliferative drug sirolimus. Upon deployment, the coating regulates the controlled release of sirolimus into the vessel wall. The drug inhibits the proliferation of vascular smooth muscle cells, directly targeting the biological process of neointimal hyperplasia, which is the primary cause of in-stent restenosis (ISR).
- **Innovation Claim:** Sinomed positioned the COMETIU system as the "world's first" self-expanding intracranial drug-coated stent system. This claim highlights its specific design for the intracranial environment, distinguishing it from repurposed coronary stents.

Feature	*Specification*
Device Type	Self-expanding, drug-eluting stent system
Indication	Symptomatic Intracranial Atherosclerotic Stenosis (ICAS)
Stent Material	Nitinol (Nickel-Titanium) Alloy
Ancillary Drug	Sirolimus (Rapamycin)
Drug Carrier	Biodegradable PLGA Polymer
MoA	Inhibition of neointimal hyperplasia to prevent in-stent restenosis

Clinical Context: Intracranial Atherosclerotic Stenosis (ICAS)

The clinical target for COMETIU, symptomatic ICAS, is a major public health challenge. It is a leading cause of ischemic stroke globally and is disproportionately prevalent in Asian, Hispanic, and African populations. The condition arises from atherosclerotic plaque buildup inside cerebral arteries, restricting blood flow. When stenosis becomes severe, typically defined as ≥70% narrowing, patients are at high risk of recurrent stroke despite aggressive medical management. Endovascular treatment with stents is a logical therapeutic option, but it has been plagued by challenges, creating a clear unmet clinical need for a more durable solution.

The “Flawed Predicate”: The Stryker Wingspan Stent

The regulatory history of intracranial stenting is dominated by the clinical performance of the Stryker Wingspan stent. This device, a bare-metal stent (BMS), provides the essential context for understanding the decisions of all three agencies. While the Wingspan can restore vessel patency, its long-term efficacy is limited by high rates of ISR.

More critically, the landmark SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) trial produced damning results. The trial was stopped early because the stenting arm, which used the Wingspan device, demonstrated a periprocedural complication rate (stroke or death within 30 days) of 14.7%. This was significantly higher than the 5.8% rate in the medical therapy arm. This high-profile failure led the FDA to severely restrict the Wingspan's labeling, limiting its use to a very narrow, last-resort patient population.

The SAMMPRIS trial cast a long "regulatory shadow" over the entire field. This single event simultaneously created two opposing forces. For the FDA, the poor performance of the only approved alternative established an exceptionally low bar for a new device to demonstrate the *potential* for a more favorable benefit-risk profile. This made it easier for a device like COMETIU, with promising preliminary data, to qualify for an accelerated development program. Conversely, for all regulators, particularly the NMPA when considering a final approval, the trial created an extremely high safety bar. Any new intracranial stent would be scrutinized against the backdrop of this prior failure, making non-randomized data appear particularly risky for a definitive marketing decision.

III. Western Regulators: Focused on Development

The FDA and EU regulatory actions are fundamentally different from the NMPA's final judgment. They represent assessments made at an earlier stage of the product lifecycle, focused on facilitating the development of a potentially superior technology.

U.S. FDA: The Impact of the Wingspan Stent

In August 2025, the FDA granted a Breakthrough Device Designation (BDD) to the COMETIU stent system. The BDD program is a voluntary pathway designed to expedite the development and review of devices that may provide more effective treatment for life-threatening or irreversibly debilitating conditions.

The COMETIU system met the two primary criteria for this designation. First, symptomatic high-grade ICAS is a life-threatening condition due to its high risk of recurrent, disabling stroke. Second, the device demonstrated the *potential* for more effective treatment. The FDA's assessment of this second criterion is not made in a vacuum; it is made relative to the existing standard of care, the deeply problematic Wingspan stent. The strong general evidence from multiple trials favoring drug-eluting stents (DES) over BMS for ICAS, combined with COMETIU's preliminary data showing a 0% ISR rate in an initial 16-patient study, provided a strong argument for potential superiority.

In our opinion, the FDA's decision was a pragmatic one: the BDD is not a marketing authorization. It is a procedural tool that provides Sinomed with priority review and more interactive communication with FDA experts. Crucially, it allowed the company to bypass an Early Feasibility Study in the U.S. and proceed directly to a pivotal trial to support a future Premarket Approval (PMA) application. The FDA's action was a calculated acceleration of the evidence-generation process, acknowledging the urgent clinical need and facilitating a more efficient path to obtaining definitive data.

EU MDR: Proceeding as Planned, Probable Post-Market RCT

Sinomed submitted its application for CE marking under the EU Medical Devices Regulation (MDR - Regulation (EU) 2017/745) in October 2024. The application is being reviewed by the Notified Body DEKRA Certification BV. As of late 2025, the application was in the final stage of technical review after the company successfully passed the mandatory on-site quality system audit.

The EU MDR has significantly elevated the requirements for high-risk Class III devices like COMETIU. It demands more substantial clinical evidence and more rigorous post-market surveillance than the previous directive. A formal clinical investigation is mandatory to confirm safety and performance. While there is no specific guidance for intracranial stents, guidance for analogous coronary stents strongly recommends randomized controlled trials (RCTs) to substantiate claims of superiority or non-inferiority. As a DES, COMETIU is also subject to consultation with a competent medicines authority, such as the European Medicines Agency (EMA), to obtain a scientific opinion on the ancillary drug, sirolimus.

The positive progress of the application suggests Sinomed's non-clinical data and quality systems are sound. However, the final determinant will be clinical evaluation. The EU MDR framework provides a middle ground between the FDA's development-focused BDD and the NMPA's final judgment. A Notified Body might grant an initial CE mark based on strong single-arm data, but this would almost certainly be contingent on a legally binding commitment to conduct a large-scale, post-market RCT as part of the mandatory Post-Market Clinical Follow-up (PMCF) plan. This "approve, then verify with an RCT" model is a common approach under the MDR for high-risk devices. The statement that the review is in its "final stage" must be interpreted with caution, as the overall MDR system is known for long processing timelines.

IV. The NMPA Pathway in Detail

The COMETIU stent's journey through the NMPA system began with promise but ended with a rejection that is, in VVR Medical's opinion, highly representative of what has become the Chinese regulatory policy.

Chronology of Key Regulatory Events

A detailed timeline reveals that the evidentiary bar for intracranial stents was already being raised by competitors before Sinomed's application was even submitted.

Date	*Jurisdiction*	*Milestone / Event*
Nov 2, 2023	NMPA	Competitor Trial 1 (ChiCTR2300077271, HeartCare) is registered. This is an RCT for an intracranial DES vs. the Wingspan stent.
Nov 22, 2023	NMPA	Competitor Trial 2 (ChiCTR2300077872, Leland Biotech) begins enrollment. This is also an RCT for an intracranial DES vs. the Wingspan stent.
April 2024	NMPA	COMETIU is approved for entry into the 'Innovative Medical Device Special Review Procedure'.
May 2024	NMPA	The NMPA formally accepts Sinomed's registration application for technical review.
August 2025	FDA	The U.S. FDA grants Breakthrough Device Designation to the COMETIU system.
October 28, 2025	NMPA	Sinomed receives a "Medical Device Not Approved for Registration" notice from the NMPA.

Sinomed’s Clinical Evidence: A Calculated Risk

Sinomed's registration application to the NMPA was based on the results of a domestic clinical trial. This study, registered on clinicaltrials.gov as NCT05217459 (but, surprisingly, not registered on ChiCTR), was a prospective, multicenter, single-arm trial designed to evaluate the device against a pre-specified objective performance criterion (OPC), or "target value".

- **Study Design:** Single-arm, non-randomized, target-value trial
- **Patient Population:** 128 patients planned with symptomatic ICAS (≥70% stenosis)
- **Primary Endpoint:** The incidence of in-stent restenosis at 6 months post-procedure.

According to Sinomed's public disclosures, the trial successfully met its pre-set endpoints. This study design appears to be a strategic choice, likely intended to accelerate development and reduce costs, a logical approach for a product in a fast-track program.

However, this choice carried a significant regulatory risk, placing a massive burden of proof on the sponsor.

The Rejection and Its Aftermath

Despite the positive trial results and the device's innovative status, the NMPA issued a "Medical Device Non-Approval for Registration" on October 28, 2025. The official disclosure from Sinomed did not state the specific reasons for the rejection but confirmed the negative outcome. The company subsequently announced an investor call to discuss the decision, underscoring the event's significance.

V. Deconstructing the NMPA Process

For regulatory professionals accustomed to the FDA and EMA, understanding the NMPA's decision requires a deeper look into the mechanics and philosophy of its premier review pathway.

The "Green Channel": Promise and Prerequisites

The "Innovative Medical Device Special Review Procedure," often called the "Green Channel," was established to encourage domestic medical device innovation and accelerate the market entry of high-value products.

- **Advantages:** For accepted devices, the pathway provides prioritized review at all stages, dedicated NMPA personnel to facilitate communication, and significantly accelerated approval timelines.
- **Eligibility:** A central, non-negotiable criterion is that the applicant must lawfully own the core technology invention patent for the product in China. An analysis of Sinomed's patent portfolio, which includes Chinese patent application CN10583335A for an "intracranial drug-eluting stent system," confirms that COMETIU met this foundational requirement. Its official acceptance into the program in April 2024 is the ultimate confirmation of its eligibility.

The Communication Protocol: Understanding Articles 18 & 19

The most critical benefit of the Green Channel is enhanced access to regulatory guidance. The NMPA has formally adopted a policy of "*early involvement, one enterprise one policy, whole process guidance, and research-review linkage*" for major innovative products. This is operationalized through specific articles in the "Provisions for Special Review of Innovative Medical Devices".

Articles 18 and 19 establish a formal, structured process for communication between the applicant and the NMPA's Center for Medical Device Evaluation (CMDE). This process provides a clear, officially sanctioned opportunity for a company to present its proposed trial design and receive feedback before execution. The formality of this protocol is a key feature. The communication must be documented in a formal record that is signed and confirmed by both parties. This transforms the discussion from informal advice into a documented event that serves as a reference for the final review.

Communication Stage	*Initiation Mechanism*	*Eligible Discussion Topics (per Article 18)*	*Regulator's Obligation (per Article 19)*
Pre-Application or **During Review**	Applicant submits "Innovation Medical Device Communication Application Form" to the CMDE	• Major technical issues • Major safety issues • **Clinical trial protocol/plan** • Summary of phased clinical trial results • Other important issues	• Promptly review the application • Inform applicant of the outcome • If approved, negotiate meeting details • Arrange and conduct the session
Output	A formal record of the communication, which must be signed and confirmed by both parties		

This formal communication protocol is a double-edged sword. It offers an invaluable opportunity to de-risk the development process by gaining early alignment on a clinical trial design. However, because the agreement is formally documented, it makes it very difficult for a company to later claim that a rejection based on trial design was a surprise. It effectively locks the sponsor into the chosen evidentiary path.

In the COMETIU case, given the project's timeline and as explained in detail further down herein, it is VVR Medical's opinion that the NMPA and Sinomed almost certainly agreed to the single-arm trial plan, despite the pre-existence of 2 ongoing RCTs initiated by Sinomed's competitors.

This formal agreement meant the NMPA's final judgment would be squarely and justifiably focused on whether the *data* from that agreed-upon plan was sufficient for a final approval, not on the plan itself.

VI. Head-to-Head Analysis: Unpacking the Divergence

The divergent outcomes for COMETIU are the direct result of applying different standards at different points in the regulatory lifecycle: the NMPA was asked for a final judgment, while the FDA and EU were asked to assess the device for an expedited development or approval pathway.

Different Questions, Different Answers

- **The NMPA Question:** Is the evidence from this single-arm trial sufficient to definitively establish a favorable benefit-risk profile for full marketing approval of a high-risk, permanent neurovascular implant?

  Answer: No. A non-randomized trial cannot adequately control for confounding variables and provides a lower quality of evidence for critical safety endpoints compared to an RCT.

- **The FDA Question:** Does this device, based on preliminary data, show the *potential* to be more effective than the currently available, deeply flawed alternative?

  Answer: Yes. The BDD is designed to facilitate the collection of the very data the NMPA found lacking.

- **The EU MDR Question:** Is the pre-market evidence sufficient for an initial CE marking, and what post-market evidence is required?

  Answer: Potentially. The single-arm data might be sufficient for an initial approval, but is very likely to be coupled with a mandatory and robust post-market RCT.

NMPA Rationale: Allowance for a High-Risk Gamble

The timeline analysis confirms that the NMPA was undoubtedly aware of ongoing competitor RCTs when it consulted with Sinomed: both RCTs were ongoing when Sinomed obtained ‘Innovative’ status.

This raises a critical question: *why would the agency agree to a single-arm trial for COMETIU?*

The answer is not a contradiction, but a reflection of the flexibility and strategic intent of the 'Innovative' pathway. The NMPA's agreement was not an endorsement of the single-arm methodology as equivalent to an RCT, but rather a **conditional** allowance for a higher-risk, higher-reward development strategy.

The 'Innovative' pathway's guiding principles of "early involvement" and "one enterprise one policy" allow the NMPA to offer customized, flexible guidance to encourage domestic innovation. In our view, by permitting Sinomed to proceed with a faster, less burdensome single-arm trial, the NMPA was facilitating one of the core goals of the pathway: speed. However, this facilitation came with an enormous, albeit implicit, condition.

In allowing this approach, the NMPA effectively placed a massive burden of proof on Sinomed. The agency was merely permitting Sinomed’s gamble: if the data from the single-arm trial were overwhelmingly positive and scientifically unambiguous—for example, showing a near-zero event rate with an exceptionally narrow confidence interval—it might be compelling enough to overcome the inherent limitations of the study design.

The agreement was on the *plan* to collect data, not a pre-approval of any data that simply met the endpoint.

Although details are undisclosed to the public, based on VVR Medical’s experience and expertise, it is our opinion that the rejection occurred because Sinomed's data, while positive, failed to clear this exceptionally high bar. Simply put, the results were likely "good," but not "incontrovertible." When the NMPA's reviewers performed their final benefit-risk assessment, they weighed the "good" but scientifically weaker evidence from COMETIU's single-arm trial against the knowledge that "gold standard" RCT data for similar devices was forthcoming. Faced with this choice, they made the conservative and scientifically defensible decision to enforce the higher evidentiary standard.

Comparative Regulatory Analysis

The following table summarizes the core differences in regulatory philosophy and requirements that led to divergent outcomes.

Feature	*NMPA (China)*	*FDA (U.S.)*	*EMA (EU MDR)*
Regulatory Stage	Final Market Approval	Expedited Development Pathway	CE Marking (Initial Approval)
Acceptability of Single-Arm Data	Rejected for final approval	Sufficient for BDD & pivotal trial justification	Potentially sufficient for initial CE marking, likely contingent on mandatory post-market RCT
Comparator Standard	Implicitly requires direct, concurrent control (e.g. Wingspan)	Flawed incumbent device (Wingspan) creates a low bar for demonstrating potential benefit	Justified best available therapy (Wingspan or medical management)
Underlying Philosophy	Decidedly conservative; enforcing global best-practice (RCTs) for high-risk devices	Risk-based and access-oriented, especially where unmet needs and flawed alternatives exist	Precautionary principle; requires robust pre-market data and mandatory long-term post-market evidence generation

VII. Strategic Takeaways

The rejection of the COMETIU stent is a powerful demonstration of a mature and rigorous Chinese regulatory system applying exacting standards to a high-risk therapeutic area. The paradox of a guided, innovative device failing at the final hurdle is resolved by understanding the profound difference between a regulator agreeing on a plan to collect data and being ultimately convinced by the data that is collected.

The NMPA's decision was not an arbitrary act but a deliberate policy enforcement. It signals a strategic alignment of its evidentiary requirements for *final marketing approval* of high-risk devices with the global scientific consensus favoring RCTs.

This case offers several critical lessons for global regulatory professionals:

- **NMPA is Stringent with Everyone, Including Chinese Companies:** With this case, featuring a prominent, listed Chinese medical device innovator, the NMPA has signaled its alignment with the highest global evidentiary standards, no matter the origin of the applicant.

- **NMPA Engagement is Nuanced:** The formal communication channels of the "Green Channel" are invaluable for aligning on trial protocols. However, this alignment is on the *methodology*, not a guarantee of approval. The burden of proof remains on the sponsor to generate data that is not just positive, but scientifically conclusive.

- **Harmonize Global Clinical Strategy:** Manufacturers developing high-risk devices should design their pivotal clinical trial programs from the outset to meet the stringent requirements of all three major jurisdictions – “design RCTs with China in mind”.

- **Monitor the Competitive Landscape:** The evidentiary standard in a given therapeutic area is not set solely by the regulator. It is heavily influenced by the most rigorous clinical programs being run by competitors. Chinese clinical trial registries are a critical source of regulatory intelligence for understanding the de facto standard of evidence the NMPA will expect.

Disclaimer: VVR International and VVR Medical declare that they have no current or prior business, financial, or advisory relationship with Sinomed or any of its subsidiaries. Neither VVR International nor VVR Medical has had any involvement in the research, development, clinical evaluation, or regulatory strategy for the COMETIU stent system. The case study presented herein is based exclusively on publicly available information, independent research, and in-house expert analyses.

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