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From Outsourced to Open Source: Denali's R-Driven Transformation in Biometrics

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ABSTRACT

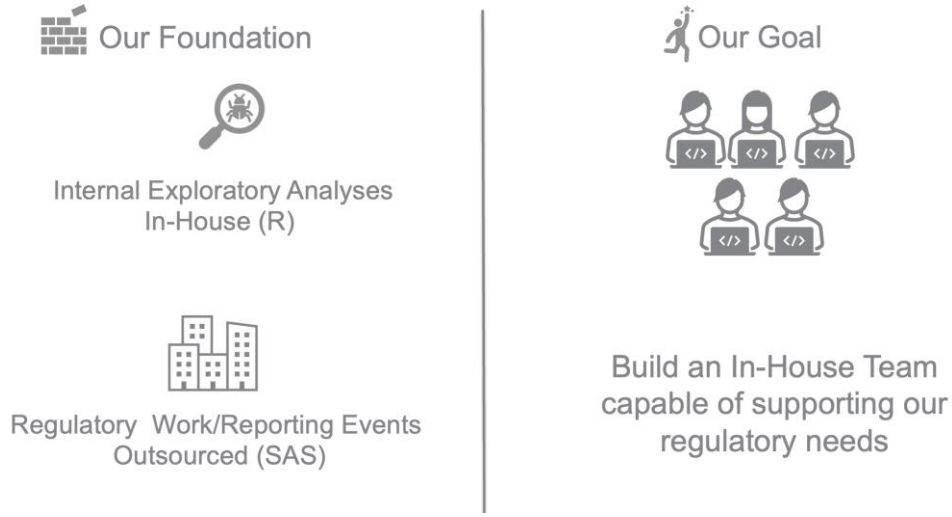
In 2025, Denali Therapeutics, Inc., a biotechnology company based in South San Francisco, submitted its first Biologics License Application (BLA) to the US FDA via the Accelerated Approval pathway. This milestone not only marked Denali's inaugural BLA submission but also the company's first Clinical Study Report in which Biometrics deliverables were not fully outsourced. Instead, Denali adopted a hybrid operating model: the analysis workload was shared between an external vendor using SAS and Denali's in-house Biometrics team leveraging R within a validated Statistical Computing Environment. By choosing the open-source R language over proprietary SAS, Denali was able to build on the shoulders of giants, leveraging pharma-specific R packages developed and shared by the broader industry through initiatives like the pharmaverse. This gave Denali a significant head start, enabling the team to perform analyses efficiently within a GxP-compliant environment, while increasing ownership of critical regulatory deliverables and building internal capability.

INTRODUCTION

Denali Therapeutics, a pre-commercial Biotech company based out of South San Francisco developing medicines for lysosomal storage and neurodegenerative diseases, embarked on a transformative journey from an outsourced biometrics model to a fully in-house R-driven environment. This paper outlines the strategic, technical, and organizational steps that enabled Denali to file its first Biologics License Application (BLA) via the Accelerated Approval (AA) pathway in May 2025. Leveraging open-source technologies such as pharmaverse, a validated R environment, and extensive process standardization, Denali successfully generated over 1,600 tables, listings, and figures spanning multiple studies. The experience underscores the power of R for regulatory submissions and serves as a role model for other small Biotech companies on how to take ownership of critical deliverables in-house.

BACKGROUND

Once dominated by proprietary SAS based infrastructure and systems, the Biometrics landscape within the pharmaceutical industry has shifted toward open-source tools, most notably R. This has been driven by regulatory acceptance, community collaboration, and the rise of packages specifically designed for clinical reporting.



For Denali Therapeutics, a mid-sized biotechnology company with multiple ongoing clinical programs on the verge of becoming a commercial company, the ability to move fast, adapt, and retain data ownership was critical. The company's biometrics organization sought to reduce reliance on Contract Research Organizations (CROs) and external SAS contractors while building internal capability for high-quality, submission-grade outputs. Whilst from its inception there was a strong R community within Denali's Biometric department; R had only been used internally for exploratory analyses; regulatory work had been outsourced and produced by experienced vendors with SAS. Looking towards the future, Denali wanted to build an experienced in-house team that would be capable of supporting

regulatory needs.
This initiative was not only a technological change but also a philosophical one. Denali recognized that investing in R would yield long-term returns: reduced vendor management overhead, increased transparency, and the ability to reinvest savings into developing internal expertise. The decision to embrace R and move work in-house represented a commitment to open collaboration and community-driven innovation. At its core, this journey was about creating a culture where biometrics professionals were empowered to innovate and entrusted to produce and deliver high-quality work to support the drug-development process.

WHAT WE DID

Denali submitted its first Biologics License Application (BLA) via the Accelerated Approval pathway in May 2025. This BLA filing marked a major milestone not only for the company as a whole but also for the Biometrics department as it demonstrated the success of its strategy to take critical deliverables in house and embracing open-source tools. The submission encompassed two clinical studies (Natural History + Phase I/IIB), an Integrated Summary of Efficacy (ISE), and a biomarker reference range study. Approximately 60% of the total outputs, including over 1,000 tables, listings, and figures, were produced internally using R, with the remainder supported by CROs using SAS.

HOW WE DID IT

The foundation of Denali's transformation was built on three key pillars: people, platform, and process.

People

Firstly, the company assembled a new specialized internal R team composed of experienced programmers, several of whom were active contributors to pharmaverse packages and members of the R Pilot Submission program. This team brought a mix of expertise in clinical study reporting and package development which enabled Denali to confidently leverage a variety of open-source packages as part of the submission and feel well versed in handling many common programming stumbling blocks.

Platform

From a systems perspective, Denali invested in a cloud-based off-the-shelf Statistical Computing Environment (SCE) designed to be GxP-compliant and expanded to support R in addition to SAS. The environment supported review workflows, access control, version tracking, and reproducibility, all core elements for regulatory readiness. A process for R package validation, a key requirement to leverage R in a GxP environment, was developed by the team. The process leverages the riskmetric package to quantify and document validation risk for R packages, aligning open-source flexibility with compliance requirements. This ensured that all packages being used as part of the submission were vetted by the team prior to use and confirmed to be functioning correctly within the system. Adapting to working in the new system posed a challenge and required a flexible and open-minded attitude.

Process

On the process side, Denali focused on programming parameterization, code reuse, and open-source package integration (e.g., rtables, logrx, tidyverse, ggplot2) which were essential to standardize output structures and scale deliverables efficiently. Leveraging open-source packages and the pharmaverse dramatically accelerated our timelines and reduced workload. With minimal time and investment spent developing our own tools and building a large library of different functions, the team was able to prioritise key deliverables and ensure high quality; a few custom R functions built on top of this and handled study-specific nuances, enhancing consistency, reliability and

reproducibility across submissions.

Culturally, the shift required close collaboration between data scientists, statisticians, and cross functional reviewers. Regular cross-functional meetings facilitated alignment, ensuring that analytical outputs met both scientific and regulatory needs. The result was an empowered, cross-trained biometrics function capable of delivering under tight timelines without reliance on external vendors.

INSIGHTS

The transition to an in-house R-driven workflow yielded several key insights:

Preparation & Planning

Early and well-planned preparation was crucial to ensure the success of the submission. Multiple dry runs were conducted to refine and finalize the outputs, ensuring that the study team was experienced and that the outputs aligned with stakeholder expectations. The successful dry runs gave credibility to the Biometrics team within the organization and convinced management that they had chosen the right path.

Vendor Oversight

It was a significant time commitment relying on vendor generated deliverables; bringing expertise in-house reduced management overhead and resulted in more efficient deliverables.

Submission Deliverables

The team took a staggered approach to delivering elements of the submission. Only working on the esub package towards the end of the submission, while this benefited the dataset and output generation timelines, earlier or parallel development of the elements required such as the cSDRG and ADRG for the submission would have streamlined this part of the process.

Growth

The internal R team demonstrated agility and ownership, delivering high-quality outputs under tight timelines. This boosted confidence within the team and increased the reputation of the biometrics organization to deliver high quality work within the company.

Regulatory responses

Transitioning ownership in-house empowered the internal team to respond efficiently and confidently to requests for information from regulatory authorities. With an internal team now experienced across almost all areas of the submission there was minimal reliance on vendors which enabled efficient and prompt responses.

Open Source

There as a significant time and cost saving by leveraging pharmaverse and other open source R packages. The team was able to build on the industry investment in this area and lay the foundations for the workflow and reporting pipeline of the company for future submissions.

THE FUTURE

Following the success of the BLA submission, Denali plans to transition all future regulatory reporting fully in-house. Ongoing investments in R infrastructure, validation frameworks, and training will further enhance team capability. Denali also intends to actively contribute to the open-source ecosystem, including future enhancements to pharmaverse and other initiatives.

CONCLUSION

Denali's transition from outsourced SAS-based reporting to an in-house R-driven environment demonstrates that small, skilled biometrics teams can leverage R to increase internal capability and produce high quality work efficiently. In addition, it shows that open-source solutions are not only feasible but advantageous for regulatory submissions and empowering teams. Through strategic investment in people, processes, and technology, Denali delivered high-quality, submission-ready outputs with efficiency, flexibility, and transparency. The experience confirms that open-source R based approaches which leverage the great work already done in this space can meet rigorous compliance standards while fostering innovation and collaboration. For biopharmaceutical organizations navigating similar transitions, Denali's journey served as a blueprint on how to successfully create an internal Biometrics team able of supporting regulatory submissions.

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