Nu-Tek BioSciences

Fueling Cells Animal Free

Variability Reduction Programs in Cell Culture Media Production: Success Through Collaboration

Key Points

1. **Variability reduction is on the rise across all aspects of biopharmaceutical manufacturing,** with the goal of increasing productivity and decreasing risks to critical cell lines.

2. **Collaboration between customers and vendors to reduce variability** can result in a fit-for-purpose culture media, specifically tailored to meet production, quality, and compliance requirements.

3. **Nu-Tek BioSciences is the market leader in Variability Reduction Program collaborations.** Nu-Tek's capabilities support a wide variety of unique customer VRP requests that directly impact process and manufacturing improvement opportunities.

Overview

The biopharmaceutical industry is one of the fastest growing sectors in the world. New treatments enter company pipelines each year, and some arenas – such as Biologics – anticipate near-exponential growth for the next decade.[1] While there is an extensive array of innovations entering this multibillion-dollar market, variability within the materials and processes used to generate these products is a constant concern. Monitoring, controlling, and reducing or removing variability wherever possible is a top priority for manufacturers. This is needed not only to ensure the production of a consistent, quality therapeutic product from the perspective of the company, but is also a key point of focus for regulatory bodies who oversee pre- and post-market applications.

To understand the critical nature of controlling and reducing variability, it is important to understand the context of where variability arises and how the industry seeks to control it throughout its end-to-end process parameters. **The following discussion covers variability, its sources, and approaches to reduce variability in development and manufacturing programs – and in doing so, also de-risk product portfolios.**

Understanding Variability in Pharmaceutical Manufacturing

The production of pharmaceutical products is a highly complex process. Not only do manufacturers require internal checks and balances through quality control, batch records, and training, but they are also required to adhere to a multitude of development and regulatory standards.[2] While the U.S. FDA is perhaps the most well-known regulatory body, other agencies across the globe also have strict requirements for pharmaceutical product development and manufacturing to protect patients. Even with the strictest company-based controls and regulatory oversight, variability is an inherent component to manufacturing. It can be introduced in many ways throughout the production process; manufacturers are required to institute controls and tolerances around this variability to ensure product safety, quality, and efficacy.

Variability can be introduced into the manufacturing process in a variety of ways:[3]

- **Manual processes.** While automation is possible for many steps in the manufacturing process, manual interventions are still needed. Most human errors are either managed or corrected with appropriate documentation and cross-checks, but it still must be considered.
- **Complex manufacturing processes.** Today's breakthrough biopharmaceutical technologies are highly intricate and deeply interconnected. Changes in timing, temperature, pH, and other steps can introduce variation into pharmaceutical products.
- **Biology.** By their very nature, cells used in production can introduce minor variations across batches of products. Controlling inputs around cells to minimize this variability is key.
- **Raw materials.** The ingredients needed to produce pharmaceutical products can introduce variation into the manufacturing process. Controlling these inputs through rigorous qualifications and direct collaboration with the supplier is important, because it helps manufacturers to understand which attributes are the most important within each raw material. Sometimes referred to as Critical Material Attributes, or CMAs, understanding these materials is the subject of intense control and scrutiny from suppliers, manufacturers and regulators alike.

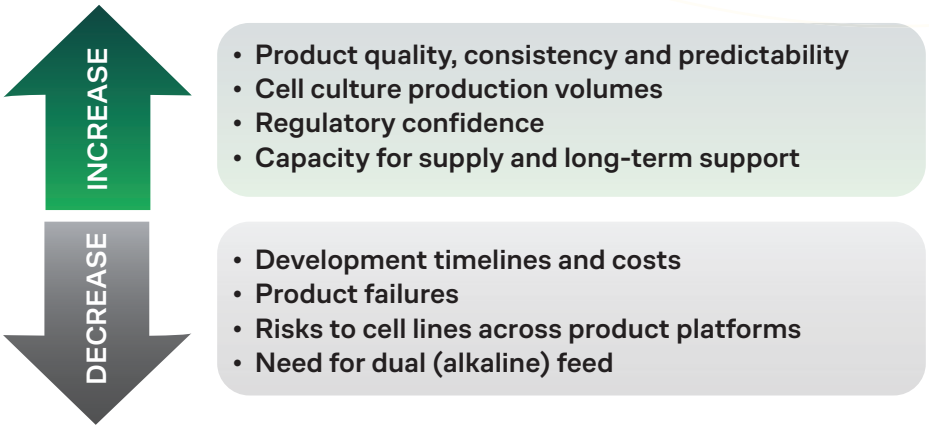


Figure 1. **The value of controlling variability of complex materials during the production of pharmaceutical products.**

The reputation of companies and their brands relies on delivering product quality and efficacy to patients. Without controls on variability, the cost to companies for lost time, product, and rework requirements can be enormous. This can delay treatment availability to patients and providers, damaging trust in a manufacturer's ability to deliver on product promises made upon approval. During the development program, developers can account for ranges seen in manufacturing steps through a rigorous process validation. Along with clinical data, these validations are typically submitted to regulatory bodies as part of the company's product approval application. However, as developers continue to manufacture approved drugs, evaluate new suppliers, and innovate new products, variability remains a constant challenge to be mitigated.

The Rise of Variability Reduction Programs

In recent years, pharmaceutical manufacturers have begun exploring new ways to further reduce even minute variability in their production process. These undertakings, often referred to as Variability Reduction Programs, or VRPs, are the result of increasing regulatory pressures, desire for differentiation, and the ability to secure cost savings from reduced product failures. Many programs are complimentary to practices such as Quality by Design principles (QbD) and are enacted early in the product development process.[4]

Production assurance and cost savings for the company can be driven by many parts of the manufacturing process. Today, special emphasis is placed on CMAs of raw materials used in production due to the significant value it can bring to production (Figure 1); whether during development, upstream to final product manufacturing, or as a direct component of drug production, variability in raw materials used to make leading pharmaceuticals are often a focal point for companies to build out VRPs.

Key Strategies for Variability Reduction

There are several key strategies that can be considered when the aim is to reduce variability (and, therefore, cost and risk) in pharmaceutical product manufacturing.[5]

- **Technology.** Building on the discussion above, technology has greatly reduced process-step related variations in the production process. By augmenting or removing the need for manual intervention to execute a given production step, manufacturers can increase the repeatability and reproducibility of manufacturing at much larger scales and with higher degrees of precision.

- **Data.** Advanced analytics and real-time monitoring have provided companies with extensive datasets. This data allows manufacturers to evaluate a manufacturing process end-to-end, assess changes over time, and apply machine learning techniques to predict where (or when) variability could be introduced into the manufacturing process. From here, abatement plans to adjust and validate production lines in real-time can be designed.

- **Training.** Improved training and expanded qualification requirements are another avenue that may reduce variability. Skilled and experienced operators can be scarce; manufacturers may find a highly competitive landscape targeting the same pool of potential employees.[6]

- **Supplier management and collaboration.**[3,7] Pharmaceutical manufacturers are increasingly reliant on suppliers for subject matter expertise, raw material management, and collaborative problem solving. Particularly in the case of raw materials that are inherently variable (animal- or plant-derived products), a deeper level of collaboration between manufacturers and suppliers is critical. While it is possible to select materials with less variability, trade-offs such as reduced performance, increased price, expanded ingredient lists to qualify, supply shortages, revalidations, and supplier pressures can increase cost and limit selection options. Manufacturers that wish to expand using existing suppliers, onboard secondary suppliers, or to control complex ingredient requirements have reinforced their need for collaboration to meet production goals. Suppliers and manufacturers benefit from open discussions regarding processes and challenges to resolve variability queries; without an open and frank discussion of needs/issues, opportunities to leverage expertise and the appropriate resources may be overlooked.

Controlling a Complex Material: The Nu-Tek BioSciences Approach

Nu-Tek BioSciences is the market leader in animal-origin free (AOF) specialty yeast extracts, hydrolysates, and plant-based peptones. Manufactured in a state-of-the-art, purpose-built facility in Minnesota, USA, Nu-Tek's products are used in a broad range of applications from vaccines and biologics manufacturing to cancer therapies, to providing the nutrient bases necessary for cell culture media. Nu-Tek's global customer base leverages the company's AOF products to remove the contamination and supply risks associated with media containing Fetal Bovine Serum (FBS) and other animal-derived components, as well as enhanced performance achieved with AOF ingredients.

Nu-Tek's products are highly complex, which benefits customers by providing similar or better culture conditions to grow living cells compared to other industrial culture media. Because of its products' complexity, Nu-Tek designed its manufacturing facility and process for real-time monitoring and control throughout the entire production process. This ensures that, regardless of the final product use, customers are guaranteed product lots that have expected nutrition and performance profiles for their specific cell culture and/or fermentation application with full visibility into the variables controlled during production. Figure 2 provides an overview of the Nu-Tek manufacturing process at its single-site facility.

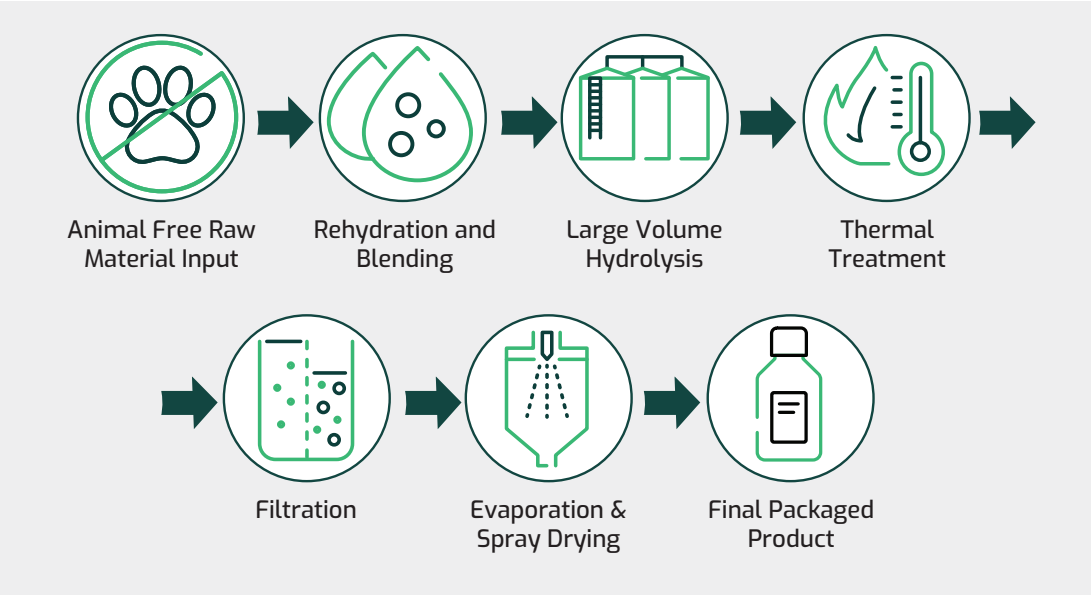


***Figure 2.*.** **Nu-Tek manufacturing process overview. State-of-the-Art monitoring and controls are leveraged at each step. All raw materials are qualified prior to use, and manufactured products must meet strict release criteria to be considered a finished good.**

Each product in the company's portfolio has its own specification. Figures 3A and 3B provide examples of specifications of CMAs captured during lot qualification and release. Additional potential criteria include, but are not limited to, pH, solubility, trace mineral and amino acid content. This allows Nu-Tek to not only ensure appropriate supply for customers, but also to provide customers with visibility into Nu-Tek BioSciences (NTB) product CMAs that can be further refined, or to match existing material attributes as part of qualifying a secondary source of cell nutrients.

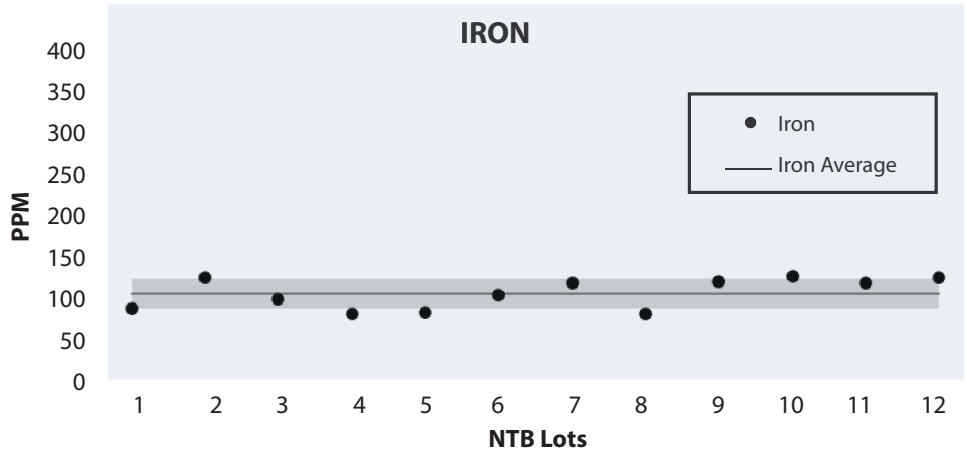


Figure 3A. **Examples of the average Iron content and variability per lot of ultrafiltered NTB soy peptone.**

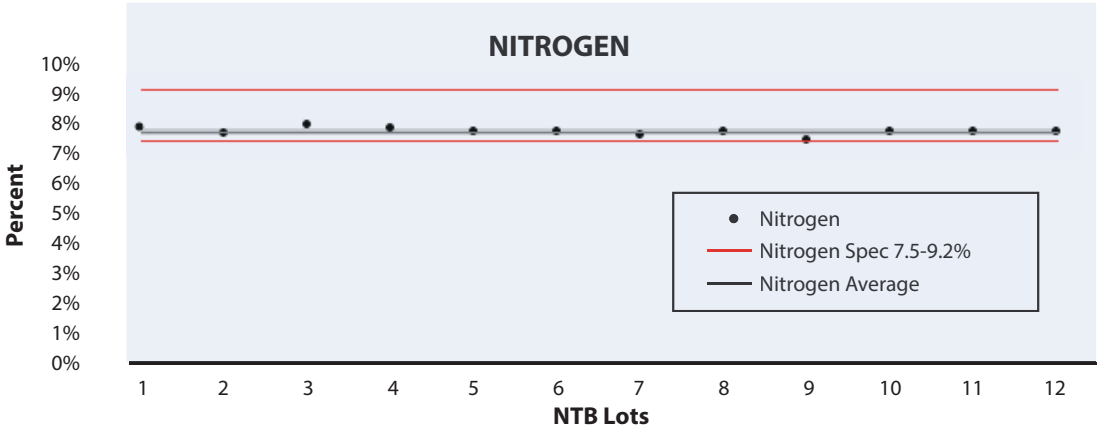


Figure 3B. **Example of the average and specification range of Nitrogen content per lot of ultrafiltered NTB soy peptone.**

Nu-Tek's state-of-the-art monitoring and controls allows customers to identify specific CMAs critical to them that, through variability reduction, could increase cell line productivity and final product quality. As the market leader in supplier-to-customer collaboration programs, Nu-Tek offers a bespoke Variability Reduction Program (VRP) pathway to support pharmaceutical product development.

Nu-Tek's Approach to VRP: Emphasis on Collaboration

Variability reduction is a highly complex process with significant performance, quality, and cost implications for both suppliers and customers. The need for control of Critical Material Attributes (CMAs) drove Nu-Tek to create the company's Variability Reduction Program (VRP). Nu-Tek has worked directly with its customers to meet VRP needs unique to specific products and platforms that would otherwise not be feasible through other suppliers. Nu-Tek's scope for VRP support includes Raw Materials, In-Process Materials, and Finished Goods, all of which follow a phased approach to evaluation. Figure 4 illustrates Nu-Tek's approach to variability reduction by each stage of a variability reduction project.

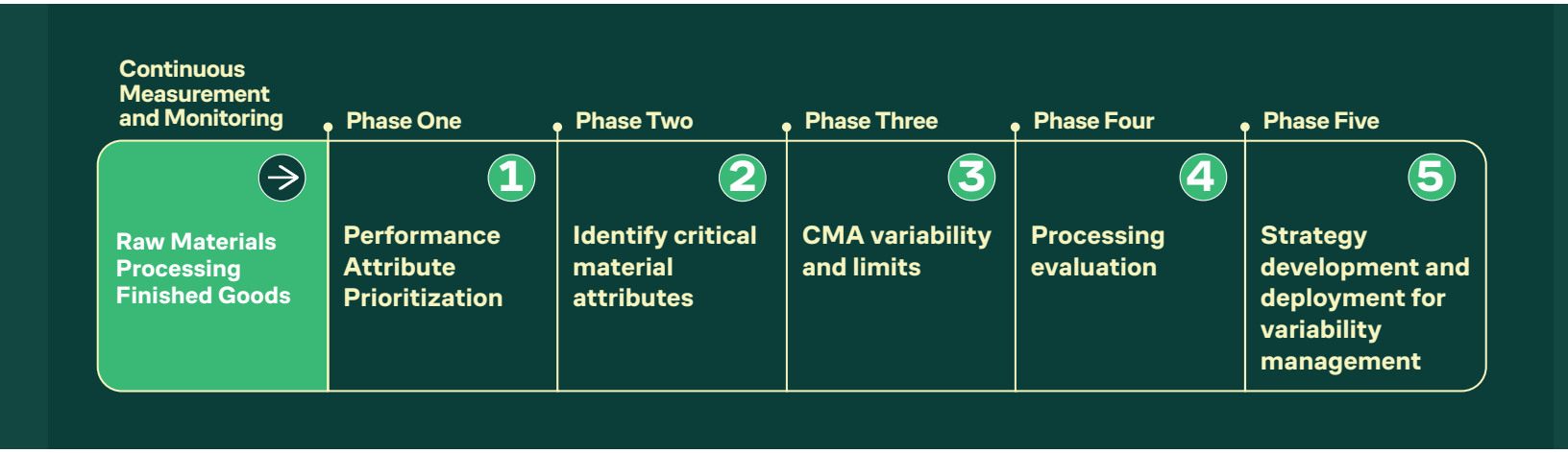


Figure 4. Nu-Tek's VRP approach by phase.

- **Phase 1:** Performance attribute prioritization. VRP projects are complex – evaluating too many variables or non-critical components of products and processes would not add value to the customer. Nu-Tek's program works with customers to identify and evaluate CMAs to ensure project scope is directly applicable to the customer's targets.
- **Phase 2:** Identify critical material attributes. Ranging from processing parameters to product profile optimization, Nu-Tek works with the customer to identify CMAs critical to a specific product or production process.
- **Phase 3:** CMA variability and limits. Once the CMAs have been identified and prioritized, Nu-Tek works directly with the customer to define the desired variability and limits required to meet the specified targets. This is an extensive process that often involves expert insights; Nu-Tek BioSciences prioritizes working directly with cross-functional teams to establish appropriate criteria.

- **Phase 4:** Processing evaluation. Nu-Tek, in partnership with the customer, evaluates the end-to-end processing parameters with respect to the specified CMAs, desired variability parameters and set limits. This includes the ability to dedicate processing time and capacity to the nuances of production-level evaluation to understand where additional controls, if needed, can be instituted to support the customers' final requirements.

- **Phase 5:** Strategy development and deployment for variability management. With the identification, prioritization, and variability parameters set, as well as a comprehensive processing evaluation, Nu-Tek BioSciences is then able to provide a bespoke development strategy for each customer. This ensures future repeatability and reproducibility for product development and commercial manufacturing support.

The VRP process is carefully monitored throughout each stage to gather invaluable data that can drive further refinement. Nu-Tek BioSciences' Variability Reduction Program also provides a dedicated team to ensure knowledge sharing and continuity of collaboration, which is necessary for manufacturers in the event of a later technology transfer or validation procedure. The following case study provides examples of Nu-Tek's approach to VRP collaborations, and its implications for the industrial leaders who take advantage of this capability

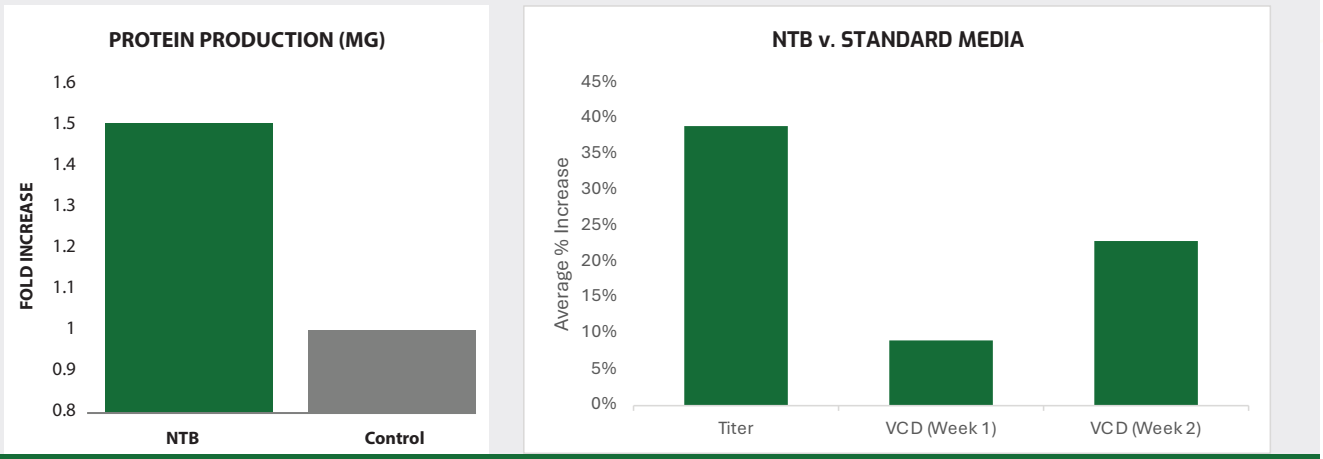
CASE STUDY

Nu-Tek's VRP Collaboration in Practice

Nu-Tek's customers are global pharmaceutical manufacturers, large scale industrial fermentation specialists, and leading pharmaceutical ingredient suppliers. Nu-Tek has worked across the spectrum of these customers to address unique needs using our VRP Process. Customer requests have served a range of functions, including, but not limited to:

- Improve final product quality and consistency
- Increase cell culture production volumes
- Reduce development timelines
- Qualify additional suppliers to alleviate issues with an incumbent
- Enhance regulatory confidence and risk mitigation
- Establish long-term partnerships and knowledge sharing with suppliers for future process improvement projects

Customers who have completed Nu-Tek's VRP program have seen significant improvements in target CMAs and productivity; ongoing VRP initiatives show similar benefits to addressing variability in complex ingredients used in culture media. Two examples (Figures 5 and 6) provide an illustration of how utilization of the Nu-Tek's VRP and in-house expertise drove results far exceeding standard media preparations.



Customers who have worked with Nu-Tek's VRP initiative have seen significant fold increase in protein production in E. coli using Nu-Tek optimized media (left), as well as improvements in end-product production, such as antibody titer and viable cell density (VCD) in CHO cells (right, Nu-Tek optimized media components v. alternative suppliers).

Protein Production

One Nu-Tek customer utilizing *E.coli* for protein manufacturing was looking to optimize their protein production and reduce the variability in specific protein attributes. This group worked with Nu-Tek's VRP team to identify key media components that may impact these elements in production. Nu-Tek provided options for the customer to evaluate in their process. This work uncovered an ingredient provided by Nu-Tek (Product "NTB") that was able to maximize the desired protein attributes while increasing protein production 1.5-fold (Figure 5).

Multi-Attribute Improvement

In another example, a Nu-Tek customer utilizing CHO cells for production of therapeutic antibodies was evaluating raw material components of their culture media. The customer's goal was to optimize multiple parameters and outputs of their culture process and aimed to leverage Nu-Tek's animal-free products in the culture media. Based on prior experience of raw material processing parameters that impact cell culture, Nu-Tek provided sample raw materials designed to improve the customer's CHO culture outputs. The customer and Nu-Tek then collaborated through the VRP program to achieve their desired CMA outcomes. Figure 6 demonstrates the increase to antibody titer and viable cell density (VCD).

Each VRP project had unique outputs for the specific customer; however, three key components, supported by Nu-Tek's Variability Reduction Program phased project design, are applicable regardless of customer request:

1. *Importance of early and open collaboration between supplier and customer.* Without building a strong and collaborative relationship, sufficient data cannot be compiled to evaluate processing and material options. Nu-Tek's priority is to establish a strong working relationship between the customer and Nu-Tek's industry experts to evaluate and resolve VRP queries to meet customer specifications.

2. *Value of tailoring solutions to specific customer needs and process requirements.* The pharmaceutical and biotechnology industries have an evolving portfolio of novel processes and products. Each requires a unique, tailored approach to variability reduction. Nu-Tek achieves this by directly collaborating with the customer, understanding the nuances of production needs, and applying expert industry experience to Nu-Tek product processing parameters to achieve the desired final specifications.

3. *Continuous monitoring and data sharing as keys to sustained variability reduction.* Without continuous evaluation of data and results, critical material attributes, processing parameters, and attainment of goals can be easy to miss. Nu-Tek proactively monitors and cross-shares data with customers to drive collective decision-making, allowing customers to have a fully transparent view into progress and project outcomes.

By focusing on providing a collaborative, tailored, continuously monitored VRP for its customers, Nu-Tek has aided some of the world's largest suppliers and biopharmaceutical manufacturers in achieving their production, regulatory, and quality goals.

The Future of Variability Reduction

Variability reduction programs (VRPs) have become a critical focus for pharmaceutical companies seeking to enhance product quality, reduce costs/risks, maintain regulatory compliance, and meet growing demand for innovative therapies. An increasing number of pharmaceutical companies are pursuing VRPs in advance of changing regulatory requirements, as well as part of their overall risk reduction strategies. By implementing strategies that address process control, critical material attributes, and supplier collaboration, the industry is making significant strides in reducing variability and improving overall manufacturing outcomes for groundbreaking therapeutics.

Nu-Tek BioSciences recognizes the critical importance of Variability Reduction Programs for customers; with direct experience in partnering with global pharmaceutical leaders in their VRPs, Nu-Tek's expertise and stage-based approach to CMA evaluation provides the critical collaboration manufacturers require to support their portfolios, variability reduction goals, and ultimately, their commitment to patients.

Pharmaceutical leaders interested in pursuing animal-free media that stand to benefit from variability reduction can learn more about Nu-Tek's offerings at www.nu-tekbiosciences.com/capabilities.

REFERENCES

1. Coherent Market Insights, *https://tinyurl.com/55wkx8pw*, January 2025
2. Center for Drug Evaluation and Research. “Current Good Manufacturing Practice (CGMP) Regulations.” *U.S. Food and Drug Administration*, FDA, www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations.
3. Challener, C. “Biopharma Takes on Raw Material Variability.” *BioPharm International*, MJH Life Sciences, www.biopharminternational.com/view/biopharma-takes-raw-material-variability.
4. Yu, X. “Understanding Pharmaceutical Quality by Design.” *The AAPS Journal*, U.S. National Library of Medicine, July 2014, pmc.ncbi.nlm.nih.gov/articles/PMC4070262/.
5. Moradi, E. “Quality Variations: Essential Strategies for Control in Pharma -.” *Pharmuni*, 27 Jan. 2025, pharmuni.com/2024/09/27/key-strategies-for-controlling-quality-variations-in-pharma/.
6. Nikulin, A. “Challenges of Pharmaceutical Industry: Key Issues in 2025.” *Viseven*, 31 Jan. 2025.
7. Challener, C. “Avoiding Excipient Variability.” *PharmTech*, MJH Life Sciences, www.pharmtech.com/view/avoiding-excipient-variability.

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