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Achieving Quality in Liquid Filling Operations with Closed-Loop Manufacturing

How Connect™ CPV Enables Adaptive Manufacturing Excellence

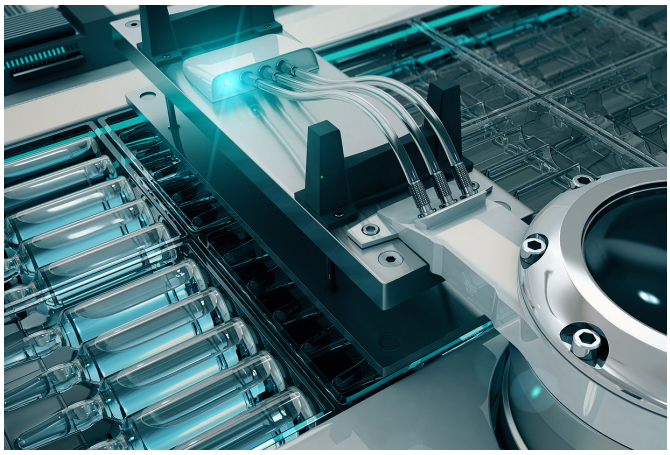
Executive Summary

Closed-loop manufacturing has become increasingly important in pharmaceutical liquid filling operations for its ability to boost quality, reduce waste, and ensure compliance. [1] In liquid filling, maintaining precise concentration levels and consistent particle distribution is essential to the safety and effectiveness of the final product—especially in injectable drugs, where even slight quality deviations can have severe consequences for patient health. Yet, traditional quality control methods often rely on manual adjustments, which can lead to inconsistencies, delays, and results that vary depending on the operator's skill.[2]

To address these challenges, there is a need for process verification software that can provide adaptive manufacturing capabilities and allow manufacturers to adjust quality parameters in real time. By leveraging data science and AI-driven controls, Mareana has devised a software called Connect™ CPV which delivers seamless, automated corrections that maintain consistency without the need for manual intervention.

In this white paper, we'll explore how Connect™ CPV's adaptive manufacturing approach meets the specific challenges of liquid filling, minimizes quality defects, and supports efficient regulatory compliance.

The Need for Closed-Loop Manufacturing



Maintaining quality in liquid filling operations is crucial to meet regulatory standards and ensure operational efficiency and patient safety. Each year, pharmaceutical manufacturers incur significant costs due to quality-related issues[3], which often trigger a series of costly steps, such as:

- **Batch quarantines** to isolate and test potentially compromised batches.
- **Extensive root-cause investigations** to trace and address the source of quality issues.
- **Corrective and preventive actions (CAPA)** to implement measures that prevent recurrence.

These processes demand time and resources, slowing down the release of safe and effective products.

In liquid filling, quality issues often arise from fluctuations in ingredient concentration and particle size distribution4, influenced by:

- **Active Ingredient Potency:** Variability in the main therapeutic component.
- **Excipients Concentration:** Changes in stabilizing agents.
- **Homogeneity of the Mixture:** Ensuring uniform distribution of all components.

Traditional manufacturing methods require operators to constantly monitor and adjust these variables manually. However, this approach has limitations:

- **Dependence on Operator Skill:** Adjustments vary by operator expertise.
- **Time-Consuming:** Manual corrections can lead to production delays or incomplete adjustments.

A closed-loop system overcomes these limitations by automating adjustments based on real-time production data, thereby reducing human error and accelerating response times.

Challenges in Liquid Filling Operations

Common issues in pharmaceutical liquid filling operations often stem from **changes in the potency of active ingredients or shifts in excipient concentrations**.[5] Keeping each component's concentration consistent is crucial when working with active ingredients and stabilizing excipients. Even slight variations can throw off the mixture's homogeneity, leading to uneven quality across batches and disrupting the entire production process.

If concentration levels fall below the required thresholds, the final product might not deliver its intended therapeutic effect. Worst, these inconsistencies can slip through undetected until after distribution, creating risks of expensive recalls, severely impacting consumer trust, and drawing regulatory scrutiny.

Controlling particle size distribution is also crucial in continuous manufacturing. Ingredients move from storage tanks to a static mixer, combined and refined by a homogenizer. If particles are too large or there are inconsistencies in particle size distribution, they can hinder the drug's absorption in the bloodstream, compromising its efficacy.[6] Unfortunately, most conventional tools can't measure particle size in real time, so manufacturers have to rely on periodic sampling and inspection—a time-consuming process that often causes delays.

To address these challenges, pharmaceutical companies are increasingly adopting **adaptive manufacturing solutions**. Adaptive systems use data-driven controls to closely monitor quality variables like concentration and particle size, making real-time adjustments to ensure the final product meets all specifications.[7]

Connect™ CPV offers such a solution, providing a closed-loop approach that enhances quality and minimizes waste by automating these critical adjustments.

The Role of Connect™ CPV in Adaptive Manufacturing

Connect™ CPV offers a fully automated solution for liquid filling operations, addressing the limitations of traditional and manually controlled processes. By integrating advanced modeling and control mechanisms directly with on-site equipment, Connect™ CPV enables real-time adjustments that ensure concentration and particle size distribution consistency.

At the heart of Connect™ CPV's approach is the **Pump Control Model**, which utilizes data from **UV-Vis spectrometry** to continuously assess concentration levels during filling. As ingredients flow from separate tanks into the mixer, the system:

- **Monitors concentration** at critical points in the process.
- **Automatically adjusts pump pressures** to maintain optimal ratios.
- **Stabilizes concentration** by reducing the flow of excipients if the main active ingredient's concentration dips.

These real-time adjustments prevent quality deviations before they become production issues, significantly reducing the need for rework or disposal of compromised batches.

Another critical innovation in Connect™ CPV is its **soft sensor[8] for particle size distribution**. Unlike conventional methods that rely on physical tools, this software-based sensor indirectly estimates particle size by analyzing data patterns from UV-Vis spectrometry. Using predictive models, Connect™ CPV can:

- **Detect particle size inconsistencies** based on concentration data and pump pressure readings.
- **Divert any affected mixture** to a waste tank when an anomaly is detected.

This approach ensures that only batches meeting quality standards proceed to the filling stage.

With its closed-loop adaptive system, Connect™ CPV minimizes dependence on operator intervention, which can introduce variability. Automated adjustments help keep the process within acceptable quality thresholds, delivering:

- **Consistent output** that enhances overall product quality.
- **Improved production efficiency** and reduced waste.
- **Enhanced compliance**, which positively impacts profitability and regulatory standing.

By automating these critical adjustments, Connect™ CPV enables pharmaceutical manufacturers to achieve efficiency and compliance with greater confidence.

Process Breakdown: Continuous Injectable Drug Manufacturing

The continuous manufacturing setup for injectable drug products is a complex, multi-stage process that requires precise control at each step to ensure both product efficacy and safety.[9]

This process typically starts with storage tanks containing specific liquid components—the primary active ingredients excipients, each serving a critical role:

Stabilizer Excipient

Prevents the formulation from disintegrating.

Temperature-Resistant Excipient

Increases the product's resilience to temperature changes, essential for maintaining integrity during storage and transport.

As the liquids move from the storage tanks into a static mixer, they are combined to achieve the desired concentration and homogeneity.

The mixture is then passed through a homogenizer, which breaks down any clumps into uniform particles, ensuring the active ingredient is evenly distributed. This step is crucial; achieving a uniform particle size allows for better absorption in the bloodstream, maximizing the drug's therapeutic effect. Once homogenized, the mixture goes through filtration and is stored in a holding tank, where it awaits final filling into vials.

One key challenge in this process is maintaining consistent concentration levels, especially when the primary ingredient tank runs low. Refilling the tank with fresh active ingredients can introduce slight concentration variations, disrupting the balance in the mixer.

If the concentration of the active ingredient falls below target levels, the final product may lack the potency needed for therapeutic effectiveness. Similarly, particle size distribution must be carefully monitored; larger particles can hinder absorption, reducing the medication's efficacy.

Connect™ CPV addresses these issues with adaptive controls. The system monitors concentration and particle size in real time, automatically adjusting the flow of each component as needed to uphold quality standards. For example, if concentration levels fall below the target threshold, Connect™ CPV automatically reduces the flow of excipients to rebalance the mixture.

Through these automated adjustments, Connect™ CPV ensures each vial meets potency standards, minimizing waste and reducing the need for manual intervention.

Data Architecture and Model Deployment

The adaptive manufacturing capabilities of Connect™ CPV are built upon a sophisticated data architecture that seamlessly integrates with on-site sensors and equipment to enable real-time adjustments. At the core of this architecture is the UV-Vis spectrometer, which continuously provides crucial data on concentration levels. This spectrometer:

- **Captures Spectrum Readings**: Continuously monitors concentration at critical points.
- **Sends Data to Connect™:** The readings are processed by Mareana's **Data Science Studio** (DSS) for analysis and real-time decision-making.

Within Connect™ CPV's data architecture, the UV-Vis spectrometer readings flow to a local server where the Pump Control Model in DSS interprets the data. This model uses predictive algorithms to:

- **Assess concentration levels** and particle size distribution.
- **Trigger real-time adjustments** when deviations are detected, ensuring the mixture returns to the desired state.

For example, if the concentration of the main ingredient drops, the model signals the pumps to **increase flow from the primary tank** and **reduce excipient flow**, effectively rebalancing the mixture in real time.

Connect™ CPV's local containerized setup, running the Pump Control Model, directly connects to the spectrometer and pumps. This configuration enables:

- **Immediate Feedback**: The model can instantly send corrective signals to the pumps, achieving rapid adjustments.
- **Secure Data Flow**: The local server securely connects to Mareana's cloud-based Connect™ platform for continuous data collection, model training, and historical analysis.

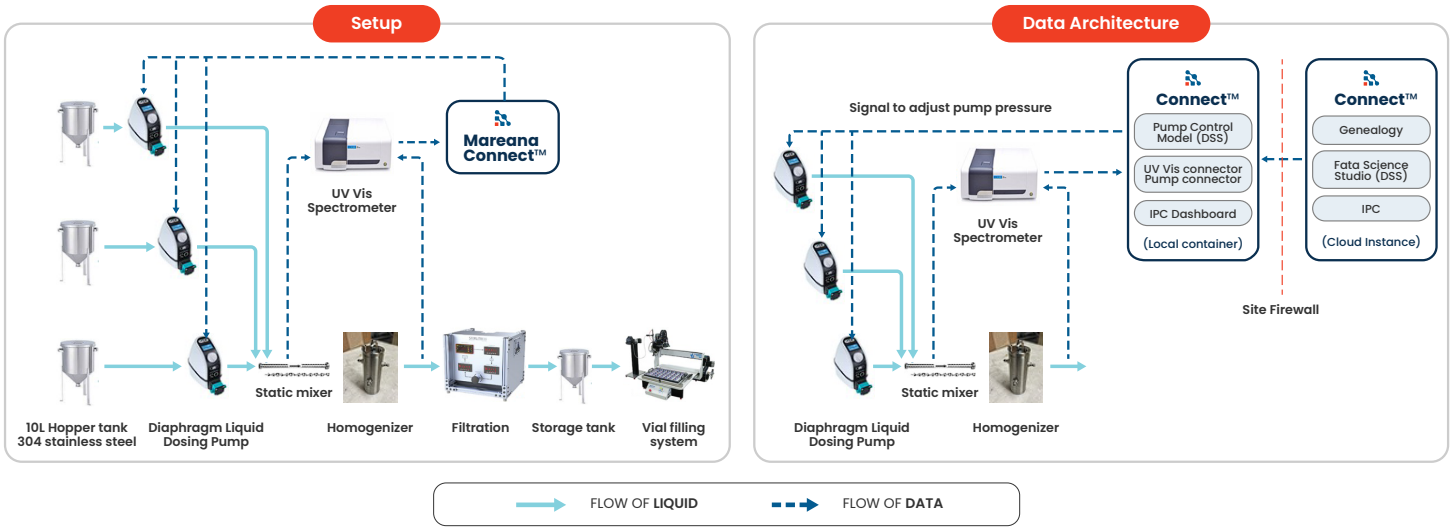
In the cloud-based Connect™ platform, the DSS allows engineers to test and update models with new data. This iterative learning process allows Connect™ CPV to:

- **Continuously refine predictive models** based on batch data.
- **Adapt to changing production conditions** over time, enhancing its accuracy in maintaining quality standards.

Through this data-driven architecture, Connect™ CPV optimizes adaptive manufacturing capabilities with each production cycle, ensuring that quality control remains precise and responsive.

Continuous Injectable Drug Manufacturing Process

Continuous injectable drug product manufacturing



Step 1: Ingredient Storage and Pumping

Three tanks hold different liquids: the main active ingredient and two stabilizing excipients. The liquids are pumped into a static mixer to combine them.

Step 2: Mixing and Homogenization

The combined mixture flows through a homogenizer to ensure even particle distribution, which is essential for effective drug absorption.

Step 3: Filtration and Storage

The homogenized mixture is filtered and then moved to a storage tank, ready for vial filling and labeling.

Step 4: Continuous Monitoring

A UV-Vis spectrometer continuously monitors the mixture's concentration and particle size. Data is sent to the Connect™ platform, which uses a predictive model to detect deviations.

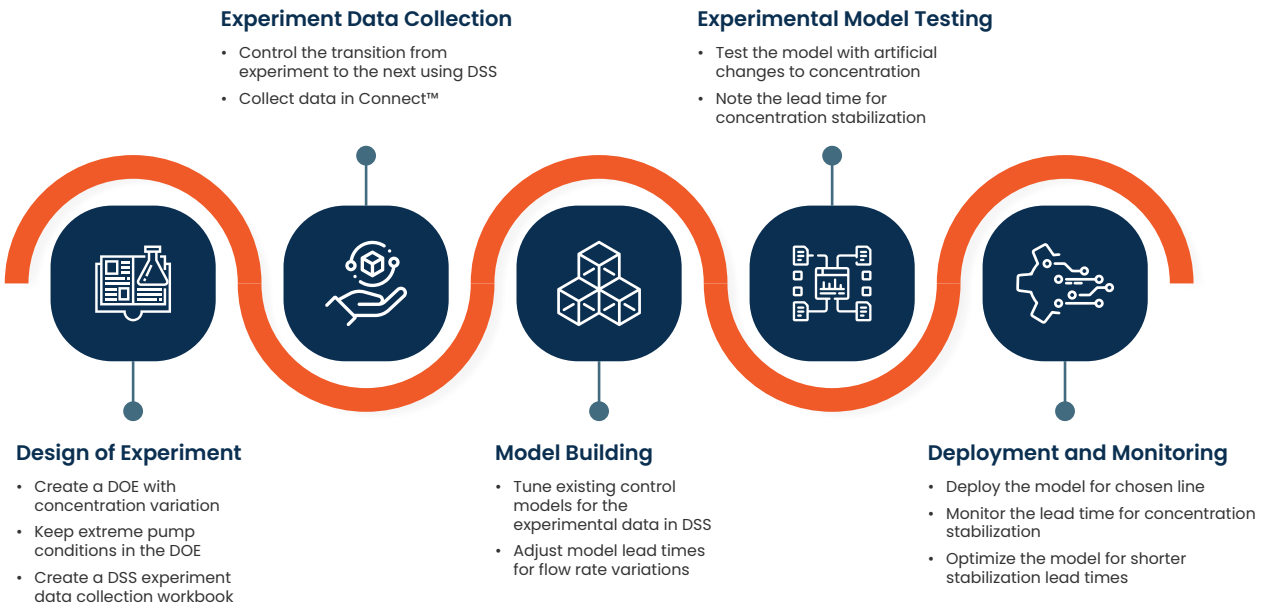
Step 5: Automatic Adjustments

If low concentration or improper particle size is detected, Connect™ CPV automatically adjusts pump pressures to correct levels in real time. Non-compliant batches are diverted to a waste tank.

Step 6: Data Storage and Optimization

All data and models are stored in the Connect™ Cloud for ongoing analysis and continuous quality improvement, creating a feedback loop to optimize future production cycles.

Model Creation, Testing, and Optimization



The strength of **Connect™ CPV's adaptive manufacturing** lies in its data-driven model, which undergoes rigorous creation, testing, and optimization to achieve precise control over concentration and particle size distribution.

This process begins with a carefully designed set of experiments, known as a **Design of Experiment** (DOE). By testing a wide range of concentration levels, pump pressures, and flow conditions, the DOE approach covers numerous real-world scenarios. Including extreme conditions helps the model gain a comprehensive understanding of the system's behavior, enabling it to make accurate real-time predictions.

Throughout the experiments, Connect™ CPV's DSS collects and manages extensive data, coordinating each phase and capturing detailed information on concentration variations and pump responses. Data points such as UV-Vis spectrometer readings, pump pressure, and flow rates are compiled to train the model, forming the foundation for predictive algorithms that regulate pumps and maintain consistent concentration and particle size.

With the experimental data in hand, Connect™ CPV's data scientists move to the **model-building phase**. Here, the initial control models are tuned and adjusted to suit the unique requirements of each liquid filling operation.

The model is optimized to minimize stabilization times and respond quickly to changes in flow rates. Testing involves introducing artificial fluctuations in concentration levels and observing the model's corrective response, ensuring it can detect deviations and make adjustments promptly to maintain quality without manual intervention.

During this testing phase, Connect™ CPV's experts monitor key performance metrics, such as the time it takes for concentration to return to target levels after a deviation. This ongoing analysis allows the team to refine the model further, optimizing it for faster response times and greater accuracy.

The finalized model is then deployed to a local server at the production facility, where it continuously monitors and adjusts pump pressures to uphold optimal quality standards.

From Compliance to Efficiency:

The Essential Benefits of Mareana's Connect™ CPV in Pharmaceutical Production

Connect™ CPV delivers a suite of benefits that directly address the challenges faced in liquid filling operations, especially those involving high-stakes pharmaceutical production. Its adaptive manufacturing capabilities provide pharmaceutical companies with the tools to improve process consistency, reduce waste, and streamline compliance efforts.

Here are the primary benefits that it brings to the table:

1. Real-Time Process Verification and Quality Assurance

Connect™ CPV continuously monitors critical quality parameters like the concentration and particle size distribution, adjusting them in real time to ensure that each batch meets precise standards. This real-time verification capability reduces the likelihood of quality deviations, minimizing the need for manual adjustments and human error-associated risks.

2. Automated Compliance and Regulatory Confidence

Compliance in pharmaceutical manufacturing is rigorous, with strict standards governing every process step. Connect™ CPV's AI-driven monitoring ensures that production stays within regulatory guidelines, while its automated data connectivity and validated product architecture (meeting 21 CFR part 11 requirements) streamline the documentation generation for regulatory reporting. By automating compliance checks, Connect™ CPV helps manufacturers release products with confidence.

3. Accelerated Time-to-Market with Reduced Waste

By proactively detecting and diverting any non-compliant product mixtures, Connect™ CPV reduces waste and shortens production cycles. The platform's adaptive controls react faster than manual intervention ever could, ensuring that only high-quality batches reach the final stages of production. This efficiency translates into faster time-to-market, allowing manufacturers to respond more dynamically to market demand.

4. Enhanced Operational Efficiency and Reduced Manual Intervention

Connect™ CPV reduces the need for constant operator oversight by automating adjustments to key process variables. The system's data-driven controls maintain quality standards with minimal human input, freeing operators to focus on strategic tasks rather than routine monitoring. This shift from manual to automated adjustments also decreases the dependency on specialized operator training, creating a more resilient and flexible workforce.

5. Long-Term Value Through Continuous Learning

Connect™ CPV's data architecture is designed for continuous improvement. As it gathers more data from production cycles, the platform's predictive models are refined to reflect the evolving nuances of each unique production environment. This iterative learning process enables Connect™ CPV to deliver ever-increasing value over time, optimizing performance as it adapts to changes in manufacturing conditions.

Conclusion

Connect™ CPV is setting a new standard for quality, efficiency, and compliance in pharmaceutical manufacturing through its adaptive closed-loop manufacturing capabilities.

By addressing critical challenges in liquid filling operations—such as concentration consistency and particle size distribution—Connect™ CPV helps manufacturers reduce waste, increase operational efficiency, and ensure that each product meets stringent quality and regulatory standards.

For pharmaceutical companies looking to enhance their liquid filling processes, Connect™ CPV offers a powerful solution that automates quality control in real time, minimizes manual intervention, and enables faster response to production anomalies.

As a cutting-edge digital SaaS product, Connect™ CPV empowers pharmaceutical manufacturers to "Make, Release, and Comply Confidently," supporting business objectives and regulatory demands. With its adaptive approach to manufacturing, Connect™ CPV drives quality and efficiency and strengthens the foundation for innovation and excellence in pharmaceutical production.

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About mareana

Mareana is a leading AI-powered software company revolutionizing manufacturing and supply chain processes within the pharmaceutical and biotechnology industries. Our flagship platform, Mareana Connect™, powers a suite of GxP-compliant solutions designed to streamline operations, accelerate batch release, reduce errors, and redefine how organizations achieve compliance and operational excellence.

Our clients benefit from significant performance improvements, such as a 33% reduction in regulatory report preparation time, a 63% faster scale-up process, and a 31% decrease in root cause analysis efforts. By integrating multiple systems into a unified, CFR Part 11-compliant platform, Mareana Connect™ enables businesses to Make Confidently, Release Confidently, and Comply Confidently.

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