ARGONAUT
MANUFACTURING SERVICES

EVERY MILLILITER MATTERS

Maximizing yield in fill-finish

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Photo courtesy of OPTIMA Pharma

The pharmaceutical industry is increasingly shifting toward more complex therapies which come with substantially higher manufacturing costs. As the cost and complexity of these products rise, so does the need for precision during formulation, sterile filtration and fill-finish operations. With high-value products costing millions of dollars per liter, even minimal drug product loss during manufacturing can waste tens of thousands of dollars. Beyond the financial impact, losses at this final manufacturing step can slow development, restrict patient supply or even delay a product progressing through clinical trials.

This whitepaper explores the most common sources of loss in drug product manufacturing and outlines some of the strategies employed by Argonaut to improve process yield and consistency in aseptic fill-finish manufacturing.

EVERY DROP COUNTS

Controlling loss in fill-finish

Many high-value molecules cannot tolerate terminal sterilization and therefore require aseptic fill-finish to manufacture an active drug product. While some product loss is inherent to fill-finish, it can be minimized by understanding the product and process in order to limit waste.

Yield preservation depends on many factors, including raw material selection, formulation stability, fluid path retention, filter holdup, fill volume consistency, destructive testing requirements and visual inspection reject rates. Left unaddressed, even small inefficiencies can snowball into significant yield loss.

In programs where every milliliter matters, manufacturing processes must be designed to minimize loss. The strategies outlined in this whitepaper reduce unit cost of drug product manufacturing and help supply critical therapies to the clinic.

MAXIMIZING YIELD

A stage-by-stage look at fill-finish

Maximizing yield begins by understanding where and why product loss happens. Critical loss points often hide in plain sight, shaped by choices in formulation, equipment and execution. Mapping these risks is the first step toward engineering processes that protect every drop of high-value product.

Loss occurs at several points throughout the fill-finish process, and the amount depends on product, platform, and process. **Table 1** outlines the primary sources of loss at each step in the fill-finish process and compares a baseline, non-optimized process to a fully optimized approach. In this example, a 5 L batch of a low-viscosity product is filled into 2R vials with a fill volume of 1 mL.

For a visual overview of where loss occurs across the process, view the infographic ↗

As shown in **Table 1**, product loss accumulates across formulation, filtration, filling and visual inspection, resulting in a significant overall impact. By optimizing performance at each stage, approximately 400 additional units can be recovered from a 5 L batch.

Recognizing product loss points is the foundation for effective equipment and process design. By pinpointing where yield is most vulnerable, drug product manufacturers can take targeted steps to preserve as much product as possible.

Table 1. Product Loss by Fill-Finish Step: Baseline vs. Optimized Process (5 L Batch, 2R Vials)

	Loss Location	Baseline	Optimized
FORMULATION & COMPOUNDING	Retention and adsorption to formulation vessel walls and fluid-contact surfaces	80 mL	**15 mL**
	Sampling	30 mL	**5 mL**
STERILE FILTRATION	Product remaining in tubing within the filter assembly	50 mL	**10 mL**
	Filter holdup from product not being flushed out of the filter or incorrect sizing of sterile filters	40 mL	**20 mL**
STERILE FILLING	Initial line prime needed to fill the tubing with product before filling begins	20 mL	**0 mL**
	Destructive weight checks for determining fill volume	100 mL	**0 mL**
	Fill volume rejects (overfilled or underfilled units)	>0 mL	**0 mL**
	End of fill line emptying which occurs once air reaches the pump and dispensed fill volume becomes inconsistent	80 mL	**<1 mL**
VISUAL INSPECTION	Visual inspection rejects	100 mL (2% reject rate)	**50 mL** (1% reject rate)
	Total volume loss:	**500 mL**	**100 mL**

TURNING DRIPS INTO DOSES

Technical approaches to maximizing yield

Preventing yield loss requires targeted, practical actions across four key areas:

- Consumables
- Fill line configuration
- Operational protocols
- Analytical testing

1. CONSUMABLES

- Use high-quality container closures
- Optimize filter size and filter membrane material
- Reduce fluid path (i.e. tubing) inner diameters

2. FILL LINE CONFIGURATION

- Reduce tubing lengths
- Perform non-GMP runs to establish accurate fill volumes and verify vacuum settings for syringes or cartridges
- Perform 100% non-destructive weights checks and “rescue dose” underfilled containers
- Fill in isolators
- Segregate crimping activity
- Minimize the number of filling heads
- Reduce or eliminate glass-to-glass contact

3. OPERATIONAL PROTOCOLS

- Minimize or eliminate line priming
- Pre-wet filters with diluent instead of drug product
- Ensure filled units are checked frequently during the filling process to identify issues early

4. ANALYTICAL TESTING

- Perform non-destructive tests when possible (e.g. non-destructive CCIT via CO_2 headspace gas analysis instead of dye ingress)
- When appropriate, use one sample for multiple analytical tests, such as pH and concentration
- Use cosmetic-reject units for analytical testing

Photos courtesy of OPTIMA Pharma

1. Consumables

Selecting the right materials can prevent loss before the first vial is filled. **Premium primary packaging components**, such as high-performance RTU (Ready to Use) glass vials, syringes, and cartridges, offer greater durability and consistency than conventional type I borosilicate containers. These components have lower likelihood of cosmetic defects like scuffs, chips, and discoloration during visual inspection and lower the risk of introducing non-product related particulates into the product.

Filter selection also plays a major role in product recovery. Filter holdup is closely tied to filter area and membrane material, so optimizing both can make a meaningful difference in yield. Low-binding membranes housed in low-volume assemblies help reduce holdup and adsorption while still supporting the required throughput without clogging or fouling. Identifying the most suitable sterile filter may require a Vmax study or compatibility study with your manufacturing partner.

Low-volume system architecture further minimizes dead space in filter and fill line assemblies to reduce holdup volume. **Reducing the inner diameter of tubing** will help achieve lower product loss; however, it may require slower filtration or filling to prevent over pressurizing the system, so this must be balanced with overall processing time, especially for temperature-sensitive products.

2. Fill Line Configuration

Effective fill line configuration is essential for reducing drug product loss. Each of the following controls directly targets a common source of yield loss.

Shortening tubing in the fill line assembly is a simple way to reduce product loss, as less tubing means less product left behind at the end of the fill. Similarly, using the fewest filling heads necessary reduces dead space and residual hold-up volume, though it may extend fill time. This trade-off must be carefully managed, particularly for temperature-sensitive products.

Before the GMP run, **adequate testing** is needed to verify accurate and consistent fill volumes and to establish proper vacuum

settings when filling syringes or cartridges. With the right vacuum control, bubble size stays small and product is not drawn into the ribs, preventing a critical defect.

100% non-destructive weight checks during DP production allow fill volumes to be monitored in real-time and adjusted if trends begin to drift. This capability can be enhanced with fill lines that have the ability to perform "rescue dosing," where low-volume units are automatically topped up before sealing. As a result, fill volumes can be set closer to the true target without risking underfilled unit rejection. This results in tighter fill-volume distribution and more usable units from the same batch, ultimately improving overall yield.

Viable (microbial) and non-viable (e.g., glass or stainless steel) particulates in containers or within the filling environment can result in critical rejects or even batch loss if not tightly controlled. The greatest source of viable contamination risk is operator presence in the filling area, which is why Annex 1 emphasizes the use of RABS and isolators to separate personnel from the aseptic process. **Filling in isolators** significantly reduces the risk of operator induced contamination and lowers the risk of sterility failures that could lead to total batch loss compared with RABS.

While both systems reduce contamination risk, isolators provide a higher level of sterility assurance. While the process for

Argonaut's fully isolator-based filling line (shown above) separates operators from the aseptic process, delivering higher sterility assurance and significantly reducing particulate risk, reject rates, and potential batch loss.

decontaminating isolators may take longer, it is straightforward as the unit is sealed and then decontaminated with vaporized hydrogen peroxide. Decontamination of RABS is a highly manual process which is harder to validate and more prone to human error. Not surprisingly, sanitizing an isolator achieves a 6-log reduction in bioburden, whereas RABS sanitization typically achieves a 4- or 5-log reduction.

The primary source of non-viable particulate is often the cap crimping station. **Segregating crimping activity** (a known source of stainless-steel particles) from the filling area will significantly reduce reject rates.

Fully automated filling systems further improve particulate control by limiting operator intervention. Each manual interaction introduces variability that may not be fully characterized and can generate particles.

For example, manipulating isolator gloves can release particulate from their surfaces. Minimizing these interventions, especially through automation, helps reduce particulate risk.

Glass-to-glass contact can result in scuffing and chipping of the surface and results in final containers being identified as having cosmetic damage during visual inspection. **Reducing and eliminating glass-to-glass contact** is an effective strategy for significantly reducing the number of final containers being rejected for cosmetic

3. Operational Protocols

Yield preservation also depends on operational strategies and training. Before filling, product is pumped into the product flow path, and a defined minimum volume is purged to remove air. On filling lines which require destructive weight checks, product is often flushed and discarded at the start of the fill as the product flow path is primed. On filling lines equipped with non-destructive weight checks and rescue dosing, **priming losses** can be eliminated entirely by filling directly into containers and adjusting volumes to target as needed.

During filtration and transfer processes, drug product can adhere to the fluid path surfaces or filters. To reduce this loss, techniques such as **pre-wetting and chase buffer protocols** are used to saturate surfaces so less product is retained, while a gas blow-down at the end of filtration and transfer helps push remaining product through the fluid path. These approaches are effective but must be carefully controlled to avoid over-dilution or introducing variability in bulk concentration.

During filling, operators should routinely **check filled units** to catch issues early and make timely adjustments to minimize rejects. For example, poor crimping may require only a small capper adjustment to reduce cosmetic defects. Syringes and cartridges should be checked frequently for product in the ribs or large bubbles to confirm proper vacuum settings. For vials, the fill needle should stop just short of the surface of the solution and rise with the fill level to prevent splashing and ensure consistent, complete transfer.

4. Analytical Testing

Analytical testing after filling is another source of yield loss. Minimizing this loss involves both clever resource management and the adoption of modern, non-destructive technologies.

Container closure integrity testing (CCIT) can contribute to product loss when performed destructively (e.g. dye ingress or helium leak detection) since it is sacrificing filled units to confirm seal integrity. **Non-destructive CCIT methods** (e.g. laser-based gas headspace analysis, vacuum decay, or high voltage leak detection) allow verification without consuming product, making these methods valuable for programs where avoiding loss is critical. FDA guidance also recognizes deterministic methods of CCIT as a superior alternative to microbial testing for confirming container closure integrity over shelf life, allowing it to replace sterility testing at intermediate stability time points while sterility testing is typically maintained at release and expiration.

Finally, **strategic resource utilization** can reduce the number of units required for analytical testing when multiple methods can be performed on a single filled unit. For example, one vial may be used for appearance, pH testing, and a concentration assay, minimizing unit consumption. Additionally, **cosmetic rejects** can still be used for analytical testing, thereby reducing the number of units pulled for destructive analytical testing and maximizing the supply available for clinical use.

Avoiding Total Batch Loss

While every sponsor of a high-value drug product wants to avoid product loss, it is far more important to avoid losing an entire batch. Sterility failures are often traced back to operator intervention, poor aseptic technique, or inadequate environmental control—risks that are significantly reduced through isolator technology, automated filling equipment, and automated material handling and transfer.

Finally, preventing batch failure depends heavily on performing adequate studies and engineering runs, something many sponsors struggle to prioritize. Filter studies, fill line testing, and engineering runs (i.e. practice runs) are essential for optimizing the process and training staff. These activities require time, money, and drug substance but they significantly reduce the chance of a failed GMP run or total batch loss and often result in better yields.

When selecting a CDMO, look for modern equipment, a track record of minimizing product loss, and flexible manufacturing capabilities, then allow the time and resources needed to properly prepare and optimize your process.

CASE STUDY

Achieving 99% theoretical batch yield

At Argonaut, our commitment to manufacturing excellence resulted in the recovery of approximately 99% of the theoretical batch yield for a high-value therapeutic. The following case study breaks down how our process, engineered from the ground up to maximize yield, delivered these exceptional real-world results.

THERAPEUTIC PROFILE

Molecule type:	Antisense oligonucleotide
Formulation type:	Aqueous, non-viscous
Batch size:	500 vials
Fill volume:	2mL fill
Container format:	2R vial

KEY CHALLENGES

High-value, low-volume	Maximizing yield from a small batch was critical.
Strict dosing accuracy	The pediatric indication demanded exceptional fill precision.
Stringent endotoxin specifications	Required due to the route of administration (intravitreal) and patient population (pediatric).

YIELD-FOCUSED INTERVENTIONS

Filtration:	Vmax study performed to optimize filter size to avoid large dead volumes in filter and losses due to oversized filters.
Fluid path:	Minimized tubing lengths on filtration and filling to avoid hold-up in the fluid path.
Filling:	The “start-up mode” feature provides extremely accurate dosing across the entire batch by eliminating priming losses. It begins by filling a single unit at a time, which allows for pump adjustments and ensures these initial units can be included as part of the usable batch.
Monitoring:	100% non-destructive weight checks and “rescue dosing” used for units identified with low fill volumes and saved by filling additional material

OUTCOME

Final Yield:	~99% of theoretical batch yield
Scalability:	Produced enough material for stability, release samples and entire clinical trial
Regulatory Impact:	No deviations with batch release achieved ahead of target release date

THE ARGONAUT ADVANTAGE

At Argonaut Manufacturing Services, we know every milliliter matters. Our fill-finish operations are built around this principle. Every detail from facility layout and equipment selection to filtration, filling, and container handling is designed to maximize yield without compromising quality or scalability.

As a result, we have achieved near-zero losses for our partners, even in complex, low-volume programs. We treat yield as a shared priority from day one to ensure drug product reaches patients, where it belongs. Minimizing product loss is possible with the right tools, mindset, and team.

Argonaut is home to many high-value drug products and complex formulations. We support flexible container formats—vials, syringes, or cartridges—across clinical and commercial phases, while protecting yield and maximizing the value of every run. Contact us to explore how our team can support your manufacturing goals and protect every milliliter.

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