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Advancing ADC Lyophilization: The Value of RheaVita's RheaLyo™ Continuous Freeze-Drying Technology for Antibody–Drug Conjugates (ADCs)

White Paper

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Introduction

Antibody–Drug Conjugates (ADCs) represent one of the most promising and technically demanding classes of biopharmaceuticals. These hybrid molecules—combining a monoclonal antibody (mAb) with a highly potent cytotoxic payload—require a manufacturing, formulation and stabilization strategy that addresses multiple interlinked challenges: maintaining mAb functionality, controlling the drug-to-antibody ratio (DAR), ensuring efficient linker design and payload release, delivering a sterile parenteral product, and protecting operator safety (especially given the highly cytotoxic payloads involved).

One often-under-appreciated critical step in the ADC value chain is lyophilization (freeze-drying). Nearly all FDA-approved ADCs to date have been formulated as lyophilized products because of the need for robust stability, parenteral administration and supply chain resilience (Antibody Therapeutics, 2025, 8, 99–110). However, conventional batch freeze-drying methods impose significant stress on fragile biologics, are time-consuming, and may introduce unacceptable process variability—risks that are amplified when dealing with ADCs.

In this white paper we explore how the continuous freeze-drying technology developed by RheaVita—the RheaLyo™ platform—offers a compelling solution for the lyophilization of ADCs. We emphasize how its operator-free, robotic, isolator-enabled architecture and rapid drying cycle (hours not days) provide enhanced compatibility with modern ADC manufacturing and containment needs, including OEB 5 (Operator Exposure Band 5) highly potent operations.

In short: "When considering the stabilization of your next ADC product, don't look any further. The RheaLyo™ controlled, continuous freeze-drying technology is all you need."

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The ADC formulation & manufacturing challenge

Development and manufacturing of ADCs is inherently more complex than that of ‘plain’ mAbs.

Some of the key issues:

- **Conjugation**: The antibody must remain functional (binding, distribution, half-life) while carrying the cytotoxic payload. The conjugation method (site-specific vs non-site-specific) influences heterogeneity, DAR distribution, aggregate propensity, manufacturability and stability.

- **Linker design**: The chemical linkage between antibody and payload influences stability (in-process and in-storage), pharmacokinetics, payload release at target site, off-target toxicity and overall safety.

- **Drug-to-Antibody Ratio (DAR)**: The average number of drug molecules per antibody must be optimal; too low and efficacy suffers, too high and you perturb the antibody’s structure/stability/target binding and raise safety risk.

- **Efficient purification**: After conjugation you must remove residual linkers, unconjugated payloads, free drug, aggregation, and other impurities—especially given the cytotoxic nature of payloads.

- **Consistent purification**: For a given DAR you must reliably reproduce the distribution, in a scalable and controllable way, with low lot-to-lot variability.

- **Reliable containment**: ADC payloads often fall under HPAPI (Highly Potent Active Pharmaceutical Ingredients) classifications. Operator safety and contamination risk (both operator-to-product and environment-to-product) must be managed. Single-use systems help, but integrative design of the manufacturing suite is critical.

- **Stable & safe formulation**: Parenteral administration demands excipients of high quality, solubility and stability. ADCs often have solubility challenges due to hydrophobic payloads—leading to aggregation, manufacturing yields issues, and compromised pharmacokinetics.
  Poor solubility → aggregate formation → decreased manufacturability or altered in-vivo behavior.

Throughout this complex process chain, choices of equipment, process architecture, containment and formulation strategy matter. The lyophilization step is especially critical because it both offers the formulation stability that many ADCs require and introduces potential stress on the molecule (freeze-concentration effects, ice-crystal formation, collapse risk, long cycle times, operator involvement). A sub-optimal lyophilization strategy can degrade product quality, increase risk and delay time-to-market.

Why lyophilization matters for ADCs

Despite the technical burden, lyophilization remains the first path for many ADCs to reach the clinic. The main drivers boil down to stability—chemical, structural, and physical.

Here are some key reasons for lyophilization:

The payload–linker is chemically fragile

The small-molecule drug attached to the antibody is usually highly reactive. Many linkers are prone to:

- → hydrolysis (water slowly snaps them apart)
- → β-elimination or other cleavage reactions
- → oxidation

By removing water and reducing molecular mobility, these reactions are slowed down.

ADCs aggregate more readily than naked antibodies

Attaching hydrophobic cytotoxic payloads makes the antibody surface patchier and more aggregation-prone. In solution, those hydrophobic patches can find each other fast. In the solid state, the molecules are locked in place, not free to collide and clump.

Hydrophobic payloads destabilize protein structure

The conjugation itself can subtly destabilize the protein fold, raising its sensitivity to:

- → thermal stress
- → agitation
- → freeze–thaw cycles
- → ionic strength shifts

Freeze-drying cuts out these stresses by giving the protein a rigid, immobilized matrix.

Broader storage and shipping flexibility

A solid cake stored refrigerated (or even at controlled room temperature for some products) is far less likely to degrade during:

- → temperature excursions
- → long shipping chains
- → mechanical agitation

For expensive, potent biologics, predictability is important.

In short, most commercial ADCs are lyophilized because the solid state protects the sensitive triad—antibody, linker, and payload—from chemical decay, structural collapse, and aggregation. The powder form boosts shelf life, keeps degradation pathways slow, and makes global distribution manageable.

Howver, traditional batch freeze-drying brings drawbacks: long cycles (often days), large equipment footprint, high operator involvement, potential for vial-to-vial variability, and complex scale-up from development to GMP. Hence the desire to be able to use a lyophilization technology that shortens cycle times, improves reproducibility, reduces operator exposure (especially for HPAPI payloads), simplifies tech transfer and generates minimal stress on vulnerable ADC molecules.

RheaLyo™ continuous freeze-drying: what it is & why it matters

RheaVita's RheaLyo™ continuous freeze-drying platform is designed precisely with these modern needs in mind. **Key features relevant to ADC manufacturers include:**

- **Spin-freezing plus thin-layer formation**: During freezing, the vials rotate along their longitudinal axis while a sterile cold gas flows over the formulation, causing the liquid to spread into a thin product layer on the vial wall. This thin layer has a large surface area which improves drying kinetics (less resistance to vapor flow, more uniform ice sublimation). As the technology page says: "The frozen vials are subsequently dried under vacuum, where individual infrared heaters provide the radiative energy transfer for fast sublimation and desorption."

- **Continuous, automated architecture**: Instead of the classic batch freeze-drying approach, RheaLyo moves the vials step-wise from freezing station to infrared-heater drying stations, governed by closed-loop PID algorithms to regulate vial temperatures and drying profiles.

- **Operator-free and isolator/robotic enabled**: For GMP lines (RheaLyo™ GMP-Flex freeze-dryers) the system integrates robotic handling under isolator conditions—from vial loading/unloading, filling to freezing, drying to stoppering—minimizing human interaction and thereby reducing operator exposure (critical in HPAPI/ADC settings).

- **Short drying cycles**: Because of the thin layer, enhanced heat/mass transfer and infrared heating, the drying process can be completed in just a couple of hours rather than days.

- **Seamless scale-out from R&D to GMP**: The same process recipe developed on the RheaLyo™ Mono systems can be transferred to the GMP-Flex lines with minimal revalidation thanks to the continuous architecture and PID controls.

- **Robust process analytical technology (PAT)**: The system supports NIR spectroscopy, thermal imaging and other sensors per individual vial to monitor residual moisture, protein conformation, solid state etc, ensuring each vial meets specification.

- **Elimination of common batch freeze-drying pain points**: For example, no silicone oil, no need for Kv (heat transfer coefficient) calibrations, no Rp (resistance to mass transfer) determinations—reducing engineering overhead and variability.

Why RheaLyo™ is particularly suited for ADC lyophilization

Linking the ADC challenges to what RheaLyo™ offers, the technology presents multiple advantages:

- **Minimal process stress**: The short drying cycle (hours not days) means the ADC molecule is exposed to freeze-concentration effects, thermal gradients, and ice-crystal formation for far less time. The spin-freezing thin layer reduces large ice crystal formation (which can damage antibodies or conjugated payloads), giving improved preservation of structure and conjugate integrity.

- **Homogeneous vials, improved stability**: The uniform freezing and controlled drying offers low vial-to-vial variability, ensuring that each ADC vial sees the same thermal and mass-transfer history—a significant advantage when the molecules are highly potent and formulation variability is unacceptable.

- **Operator safety / containment compatibility**: ADC manufacturing often needs OEB5 containment (operator exposure band 5) because of the potent payloads. The robotic, isolator-based, operator-free architecture of GMP-Flex lines helps meet stringent operator-safety requirements while maintaining aseptic process integrity.

- **Scalable for high-value, moderate throughput products**: Many ADCs are high cost, low volume products (e.g., batches in the tens or hundreds of thousands of vials rather than millions). The RheaLyo™ GMP-Flex series supports flexible production capacities (see capacities below) and is ideal for these kinds of modality where capital-intensive large batch processing doesn't make sense.

- **Tech transfer friendly**: Given the complexity of ADC development, being able to move from R&D to GMP with minimal revalidation is a huge cost & time advantage. The fact that RheaLyo™ was designed for seamless scale-out supports accelerated time-to-clinic. Many months of development time can be saved, pulling in millions of revenue under exclusivity.

- **Regulatory alignment**: The automation, PAT, continuous manufacturing and elimination of operator intervention align well with modern regulatory expectations (for example, trends in EU GMP Annex 1 emphasizing minimization of operator involvement). The system is optimized for high-value biologics and seems designed with quality and compliance in mind.

Production capacity and fit for ADC use-case

For many ADC programmes, the manufacturing volumes do not justify hundreds of millions of vials per line. According to RheaVita's published specs:

→ The RheaLyo™ GMP-Flex lines **support capacities from ~100,000 up to ~2 million vials per year** in typical configurations.

→ The scale-out architecture (Mono → Multi → GMP-Flex) means that **you can start with low volumes and scale up without wholesale redesign**. Given that many ADCs move from early-phase low volume to larger but still moderate volumes, this flexibility is a major plus.

Therefore: for high-value ADC drugs requiring production capacity of less than ~2 million vials per year per production line, RheaLyo™ is a very good match.

Operational and strategic value proposition

From an operational and strategic standpoint, the reasons to consider RheaLyo™ for your next ADC program are compelling:

- **Faster process development and turnaround**: Being able to freeze-dry in hours means more development runs, faster optimization of formulation and process, and quicker decisions in your ADC pipeline.

- **Reduced risk of product degradation or stability failures**: By reducing cycle time, optimizing crystallization speed and enhancing uniformity, you reduce risk of hidden damage to your conjugate, improve batch homogeneity and thus increase predictability of stability and shelf-life.

- **Operator-safe and containment-friendly design**: If your payload is OEB5 or otherwise highly potent, the operator-free robotic/isolator design significantly reduces safety risk and supports integration into a high-potency manufacturing suite.

- **Lower capital/time burden than large batch lyophilizers**: The continuous architecture supports lean facilities, potentially smaller footprint, less downtime between batches, and more efficient utilization of equipment.

- **Scalability aligned with high-value/low-volume business models**: Many ADCs are niche or targeted therapies; you don't want oversized manufacturing capacity. Having a system tuned for smaller volumes (<2 million vials/year) makes economic sense.

- **Regulatory and tech-transfer friendly**: With PAT, vial-level monitoring, validated PID control loops, and minimal scale-up revalidation, the route from lab to GMP becomes smoother, saving time and cost. Dossiers based on continuous manufacturing receive a much faster review time at the FDA, based on a self-audit.

- **Future-proofing your lyophilization infrastructure**: Investing in a continuous freeze-drying platform positions you for next-gen modalities (e.g., mRNA, LNPs, viruses) and ensures you're not locked into outdated, slow batch freeze-dryers.

Considerations & implementation tips for ADC programs

While RheaLyo™ presents an excellent fit for many ADC lyophilization needs, thoughtful implementation is essential. Some guidance:

- **Formulation compatibility**: Although thin-layer spin-freezing increases drying speed, you still must ensure that your ADC formulation (antibody + linker + payload + excipients) is compatible with the freezing behavior (ice crystal morphology, collapse temperature, residual moisture targets). Early feasibility studies using the Mono system are strongly recommended to define critical quality attributes (CQAs) and process parameters.

- **Containment integration**: If your facility is dealing with OEB5 payloads, make sure the full fill/finish/lyo line (including RheaLyo™) is integrated within your HPAPI containment suite, and that the robotic/isolator components are validated for the relevant containment level.

- **Tech transfer discipline**: Although RheaLyo™ simplifies scale-out, you must ensure that your process recipe (freezing rate, spin speed, IR heater power, vacuum profile) is fully documented and validated on the GMP-Flex line.

- **Capacity planning**: Confirm your expected annual vial throughput. If you're comfortably under 2 million vials/year per line, RheaLyo™ is a good fit. If you anticipate much higher volumes, you may need to consider multiple lines or alternative architectures.

- **Stability program alignment**: Align the lyophilization process with your stability objectives (residual moisture, cake appearance, protein/payload integrity over time). Given that ADCs often require long shelf-lives, make sure data packages from the RheaLyo™ dried product meet your regulatory expectations.

- **Risk mitigation**: While continuous processing reduces many risks, you still need to manage transition-in/out of the continuous dryer, ensure cleaning/validation of the robotic stations, monitor process drift, and maintain audit trails for PAT/automation systems.

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Conclusion

The rise of ADCs as cornerstone therapeutics has created manufacturing and formulation demands that traditional tools struggle to meet. Lyophilization—being essential—has often been a bottleneck: long cycles, high variability, operator-heavy, and sub-optimal for HPAPI/ADC contexts. The RheaLyo™ continuous freeze-drying technology from RheaVita offers a compelling path forward: operator-free, robotic/isolator-compatible, ultra-rapid drying in hours not days, and designed for scalable transition from R&D to GMP with minimal revalidation.

For ADC developers looking to stabilize high-value, potent molecules, and manufacture them safely, reliably and at the right throughput scale (under ~2 million vials/year per line), RheaLyo™ presents a strategic advantage. The technology aligns strongly with high-potency containment requirements, time-to-clinic pressures, formulation fragility needs, and modern regulatory expectations around continuous manufacturing.

When considering the stabilization of your next ADC product, don't look any further. The RheaLyo™ controlled, continuous freeze-drying technology is all you need.

By choosing a lyophilization platform that fits both your molecule's fragility and your business model's scale, you reduce risk, save time and preserve product integrity—so you can focus on delivering therapeutic value to patients, not wrestling with process bottlenecks

Disclaimer

This white paper draws on publicly available information from RheaVita and current industry context. Specific process implementation should be validated internally with your formulation, payload and manufacturing context.

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