

GMP RIVA KEY FEATURES FOR REGULATORY COMPLIANCE



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RIVA by ARxIUM prepares syringes and IV bags in an aseptic ISO Class 5 environment and provides the highest level of medication safety, quality and monitoring. RIVA is the first and only IV automation system designed to be used in 503B and central-fill facilities by integrating environmental monitoring on top of the proven RIVA high-capacity IV compounding system. The GMP RIVA configuration allows pharmacies to implement proven safe and efficient loading and preparation processes to compound a wide range of medications in a tightly controlled and actively monitored system. This configuration includes continuous real-time environmental monitoring and logging functions. RIVA addresses reliability and safety concerns associated with manual sterile compounding practices, and helps facilities meet the rigorous quality and environmental monitoring standards required by today's regulations.

503B Outsourcing Facilities are required to follow certain standards and FDA Guidance regarding the environmental monitoring and quality processes under which they conduct sterile compounding. Health system central sterile compounding facilities, even if they choose not to register as 503B facilities, should consider following the same guidance because it is promulgated to protect the public health from unsafe practices. Batch compounding contains numerous opportunities for process errors and viable particle contamination that could lead to patient harm. A vast number of FDA guidance documents surrounding sterile compounding are available at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm393571.htm>.

The GMP RIVA system is a stand-alone system but can also integrate with existing clean room environmental monitoring systems. RIVA provides direct input to the monitoring system about its current operational status. For example, the system automatically records if RIVA is in production or if its doors are open. It also logs when RIVA is being cleaned, which eliminates the need for users to manually record the activity. In addition to alerting and/or stopping compounding if out-of-specification environmental conditions occur, the GMP RIVA also provides the ability to document door opening and other interventions within the compounding cell when they occur without the need for another logging system. The GMP RIVA includes extensive reporting capabilities, including particle counts, pressure differentials, temperature, humidity, door opening events, cleaning records, alert/alarm events and operator

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response, pedigree data on every dose prepared, and RIVA dose productivity metrics. These reports allow facilities to quickly obtain production and environmental monitoring data regarding every dose prepared by the RIVA system.

The GMP RIVA configuration supports the intent of USP and FDA requirements regarding sterile compounding in two ways:

1. It provides a standardized method for sterile compounding processes that minimizes risk of errors. The base RIVA configuration does this today using multiple technologies to positively identify the materials and ingredients used in a preparation, then performing compounding within an ISO Class 5 environment with first air protecting each critical site.
2. The GMP configuration adds enhanced monitoring and control capabilities to meet the following FDA requirements for a high-quality 503B compounding environment. Where appropriate, the pertinent references from FDA are noted.

“Operations and appropriate written procedures designed to prevent microbial contamination include a well-defined and documented program for environmental monitoring that evaluates the potential routes of microbial contamination of the human drug that could arise from the air, surfaces, process, operation, and personnel practices (see §§ 211.42(c)(10)(iv), 211.100, 211.113(b)). The program should contain an appropriate detection component(s) to verify state of control of the environment. However, environmental monitoring equipment should not interfere with aseptic operations (e.g., instruments should not interfere with validated and appropriate airflow patterns).” —Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act - Guidance for Industry (lines 388-395 with particulars defined in lines 395-413).

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The GMP RIVA provides multiple integrated instruments to meet the environmental monitoring requirements, and these are managed through interfaces between the instruments, controller software, and RIVA.

Airborne particle counters:

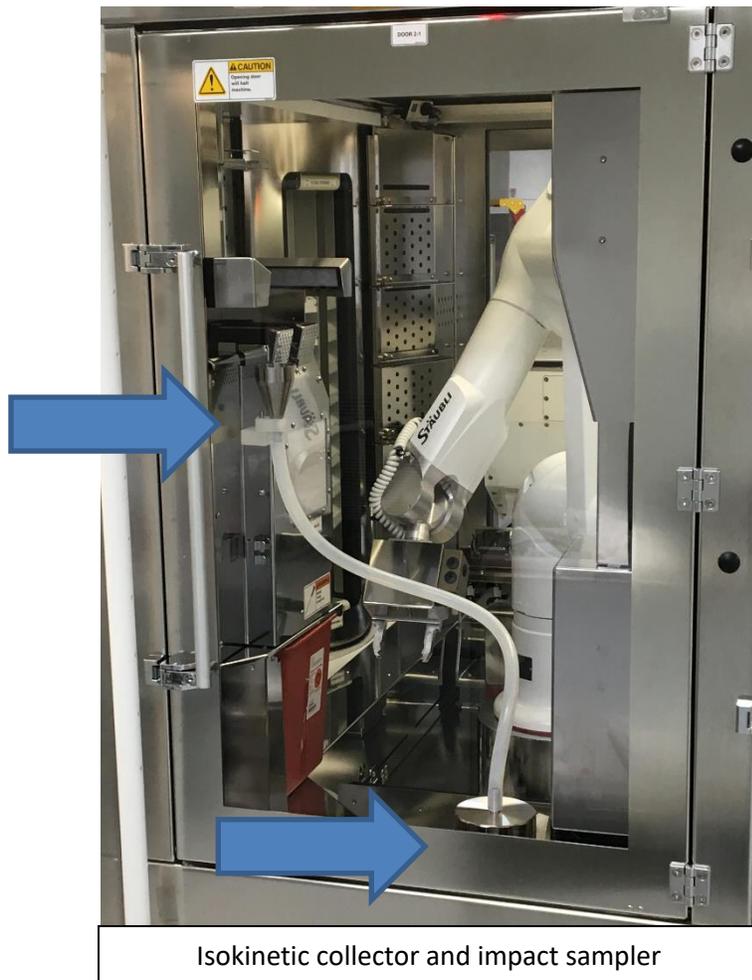
GMP RIVA contains *four* two-channel (0.5 and 5 micron) particle counters. One is located in the inventory area at the lower rear wall that has been determined to provide a worst-case monitor during carousel movement. Within the GMP RIVA compounding cell, there are three two-channel particle counters located at the critical sites: syringe capping station where sterile tip caps are exposed, the reconstitution bag-draw station, and the vial-draw / bag-dose injection station. Particles are collected through a series of isokinetic funnels (IKFs) that are coupled



with a discrete particle counter to provide continuous particle monitoring of the compounding cell. The IKFs are located adjacent to the critical sites, and smoke testing is used to demonstrate that they do not interfere with smooth airflow at the critical sites. The particle counters run continuously and send particle count data into the control software which checks the particle level against alert/alarm level settings.

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Isokinetic collector and impact sampler

Viability impact sampler:

The GMP RIVA contains an integrated airborne particle sampler that draws in cell air across a growth media plate. The impact sampler collector mounting points are located adjacent to the same three stations as the particle counters; the syringe capping, reconstitution bag-draw, and vial-draw / bag-injection stations.

Plates are loaded into the sampler by opening the door at the sampling location, which triggers a door-open event in the monitoring system so that the operator can log the intervention reason. Airflow and pressure are maintained and protect the interior environment and the sampling plate during the loading

operation.

Viability particles that impact the growth media plate can be identified after incubation and the potential origin then identified. Based on findings of the investigation, personnel, facility, processes, and the cleaning/disinfection program can be adjusted to prevent future viable incursion.

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Top Mount Signal Tower

Alarm Tower: If an excursion occurs, the operator is alerted through configurable audible and visual signal tower alerts (for example, green = OK, yellow = in limit but minor elevation, yellow+red+1 audible alarm = one out of specification excursion, red+continuous audible alarm = three sequential out of specification excursions). RIVA can be configured to respond to the alert/alarm levels to halt compounding when one or more out of specification limits are exceeded. RIVA will not



Side Mount Signal Tower

allow compounding to resume until the environmental monitoring system has detected that the state of control has been achieved.

“HEPA filters should be qualified to provide appropriate air quality and be periodically maintained and tested to ensure intended air quality. Discolored, dirty, or damaged HEPA filters should be repaired or replaced.” —Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act - Guidance for Industry (lines 303-305).

RIVA HEPA filters are readily accessible and can be inspected as part of the biweekly Preventive Maintenance program. Both the upper surfaces (facing the room) and inner surfaces (delivering clean air into the compounding cell and inventory storage area) can be directly or indirectly (using a high-resolution camera, for example) visualized for damage or excessive particulate build up. RIVA prefilters are easily removed without special tools and can be changed in minutes. RIVA HEPA fan-filter units, in the event of damage or exceeded lifespan, can be changed out by simply releasing the unit latches, lifting out the old unit, and latching in a new unit.

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“Temperature and humidity must be maintained in cleanroom areas; such controls are critical to reduce microbiological growth (see § 211.46). A specification for humidity should be established considering that higher humidity supports microbial growth, while too little humidity can cause problems with static electricity (which may be particularly problematic when working with powders) and may lead to increased particulates.” —Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act - Guidance for Industry (lines 307-311).

The GMP RIVA has two temperature/relative-humidity probes to continuously monitor both the inventory storage area and the compounding cell. The probes are located in “worst-case” locations – the inventory area is monitored directly in the clean air stream that impinges on stored drug vials. This helps ensure that medications are stored prior to compounding in an area that meets the temperature limits defined by USP Monograph, FDA requirements, and drug manufacturers. The probe for the compounding cell is located in the airflow drawn across the vial parking area where in-process vials are held. The temperature and humidity limits are fully configurable in the control software to provide four alert/alarm levels for both above and below specification measurements. RIVA can be configured to respond to these alert/alarm levels by any combination of on-screen alerts, audible and visual signal tower(s), or automatic halting or all compounding when alarm levels are exceeded for a certain amount of time.

“...a system for environmental monitoring must include the establishment of pressure differential limits (see § 211.42), and control systems should include built-in alarms to detect excursions.” —Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act - Guidance for Industry (lines 315-317).

RIVA continuously monitors and adjusts the air intake and exhaust rate through dual control systems to maintain the differential pressure at the defined set point. During inventory loading or cleaning processes, the air flow rate is adjusted to maintain positive pressure inside the inventory area and compounding cell to prevent airborne particle ingress, and provide an additional flow of filtered air across the inner-outer boundary (air curtain). On-screen, audible, and visual alerts/alarms are presented when pressure differentials fall outside the set point. RIVA continuously logs timestamped pressure differentials and includes the running queue identifier number in the event that investigation is required in relation to an excursion.

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“Labels must contain required information, and labeling operations must include controls to prevent mix-ups; furthermore, procedures must be developed to ensure these requirements are met (§§ 211.122, 211.125, 211.130, 211.134).” —Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act - Guidance for Industry (lines 1171-1173).

The GMP RIVA uses software-driven controls to generate, print, and affix a label to the finished dose. Because of this integration, it is possible to eliminate the documentation typically required to reconcile printed labels and used and/or extra labels. Because RIVA prints, applies, and checks the labels prior to outputting the dose, manual processes are not needed to check, apply, and double check that the label is correct. RIVA labels are built once, validated, and then print the same data each time a particular dose is compounded. RIVA doses and labels are serialized, and have customization capabilities that the system administrator can use to change NDC, storage conditions, expiry periods, and supplemental label text. RIVA is track-and-trace ready by already serializing every dose uniquely. With the use of 2D barcodes, it is possible to encode lot and expiry if/when that is required by regulatory bodies. Sample bag and syringe labels are provided below.



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The GMP RIVA integrated monitoring, sampling/collecting, alerting and reporting processes deliver facility-specific and real-time oversight of the RIVA sterile compounding conditions. These key features assist in ensuring the compounding cell remains in an enhanced level of aseptic control and provides the 503B compounding pharmacy with a superior automated/integrated mechanism to meet or exceed current regulatory specifications.

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