APPLIED PHYSICS

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QUALIFICATION PROTOCOL

CRF6 Airflow-Tracer Qualification Protocol

Finished-device verification of ultrasonic frequency, droplet-size distribution, plume thermal neutrality, gravitational drift, source momentum, and comparative airflow-tracer fidelity

Prepared by Applied Physics

Document No. AP-QP-CRF6-001 | Revision 1.0 | August 2026

External/controlled use: protocol template for Applied Physics or an independent qualified laboratory. Site quality approval is required before execution when used as GMP evidence.

Document purpose	Client-facing scientific and engineering support for pharmaceutical airflow-visualization qualification and regulatory correspondence.
Regulatory posture	Supports a scientifically defensible suitability rationale; does not claim FDA approval, certification, or site-specific compliance.
Controlled claim	Ultrasonic atomization can produce micron-scale water droplets that function as passive/operationally neutrally buoyant airflow tracers when the complete release system is qualified.
Device-specific status	CRF6 nominal design basis is approximately 1.65 MHz and 4-8 micrometer fresh generated droplets. Direct finished-device metrology is addressed by the companion qualification protocol.

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1. Purpose

The purpose of this protocol is to generate finished-device evidence demonstrating whether the tested CRF6 configuration functions as an appropriate passive airflow tracer for pharmaceutical airflow-visualization studies. The protocol is designed to close the device-specific evidence gaps identified in AP-TR-CRF6-002.

2. Scope

This protocol applies to a defined CRF6 serial number and a defined release configuration. The qualification is configuration-specific: changes to outlet, hose length/diameter, wand/nozzle, fan setting, fog-output setting, transducer/driver design, or other elements that can materially affect droplet or plume behavior require documented assessment and, where appropriate, partial or full requalification.

3. Regulatory and Scientific Basis

- FDA aseptic-processing guidance requires in-situ airflow-pattern analysis under dynamic conditions and documentation of interventions/equipment effects. [1]
- FDA 2026 warning letters specifically call for proper smoke-study practices, giving neutrally buoyant media as an example, and separately criticize poor source movement and blocked visualization. [2-4]
- Peer-reviewed literature demonstrates ultrasonic water fog as an airflow visualization medium and 1.65 MHz ultrasonic generation of 4-5 micrometer water droplets suitable for gaseous-flow PIV. [5,6]
- Approximately 6 micrometer water droplets have been used as passive gas-phase PIV tracers. [7]
- A 1.7 MHz ultrasonic nebulizer study shows evaporative cooling can make the carrier plume negatively buoyant, establishing the need to test the finished plume rather than assume suitability from particle size alone. [8]

4. Responsibilities

Role	Minimum responsibility	Approval / record
Test Engineer	Execute protocol, record raw data, identify deviations	Initial/date each test section
Metrology / Laboratory	Operate calibrated instruments, preserve raw data and calibration records	Instrument IDs and calibration certificates
Applied Physics Engineering	Confirm tested configuration and controlled design	Engineering review

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Role	Minimum responsibility	Approval / record
	specification	
Quality Unit / Client QA	Approve protocol, deviations, acceptance criteria, and final conclusion	Final approval when used as GMP evidence

5. Test Article and Configuration Record

CRF6 serial number
Firmware/control revision
Ultrasonic driver revision
Nominal design frequency
Water type / lot / conductivity
Water temperature at start
Ambient temperature
Ambient relative humidity
Outlet configuration
Hose ID / length
Wand/nozzle configuration
Fan and fog-output settings

Note: Component-level traceability shall be maintained in controlled manufacturing records and made available when required by an applicable quality agreement, investigation, or regulatory request. Controlled manufacturing traceability should remain available internally.

6. Required Instrumentation

- Frequency counter and/or oscilloscope with bandwidth appropriate to approximately 1.65 MHz and a documented calibration status.
- Validated droplet-size measurement system suitable for wet 1-20 micrometer aerosols (e.g., laser diffraction, phase-Doppler method, or another scientifically justified method).
- Calibrated fast-response temperature probes or thermocouples; accuracy and response time sufficient to resolve plume/ambient differences.
- Calibrated air-velocity instrumentation appropriate to the expected 0-1 m/s range and outlet-jet measurements.
- Still-air test enclosure or room with documented background air motion sufficiently low to resolve millimeter-per-second vertical drift.

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- High-resolution video with fixed scale/grid and synchronized time reference.
- For comparative testing: controlled airflow rig and accepted reference tracer; PIV or equivalent quantitative flow-field method is preferred where available.

7. Predefined Acceptance Philosophy

FDA does not publish a numeric droplet-size, Stokes-number, temperature-difference, or settling-velocity criterion for smoke-study media in the cited sources. Therefore, the protocol uses a combination of literature-grounded engineering criteria and direct comparative performance. Any numeric acceptance limit identified as "provisional" below must be approved before execution and may be tightened by the client quality unit.

> **Primary acceptance principle: the tested CRF6 configuration shall demonstrate that tracer-induced gravitational, inertial, thermal, and source-momentum biases are small enough that the tracer faithfully represents the airflow features relevant to the intended smoke study.**

8. Test 1 - Ultrasonic Drive Frequency Verification

8.1 Procedure

1. Operate the CRF6 at the production configuration and representative water level.
2. Measure electrical drive frequency at an approved non-invasive or engineering test point under load.
3. Record frequency at startup, after 5 minutes, after 15 minutes, and at the end of a representative run.
4. Repeat at minimum and maximum qualified fog-output settings if the drive architecture changes frequency with control setting.

8.2 Acceptance

Acceptance: all measured values shall be within the controlled CRF6 engineering frequency specification. The nominal design target is approximately 1.65 MHz; the exact production tolerance shall be established by Applied Physics Engineering before execution. Do not invent a tolerance after reviewing results.

9. Test 2 - Finished-Device Droplet-Size Distribution

9.1 Sampling locations

- At the qualified outlet/wand release plane.

- At one representative downstream distance (recommended 0.25-0.5 m) where practical.
- At an additional downstream distance representative of the actual application if residence time is material.

9.2 Procedure

1. Condition the device and environment to the predefined test conditions.
2. Acquire at least three replicate distributions at each sampling location and operating setting.
3. Report D10, D50, D90, and D32/Sauter mean diameter when the selected instrument/method legitimately supports those metrics.
4. Record the full distribution, not only a single average value.
5. Document water quality, temperature, relative humidity, fan setting, fog-output setting, and sampling distance.

9.3 Acceptance

Provisional product target: measured fresh-droplet distribution should substantiate the published CRF6 nominal 4-8 micrometer claim. Final acceptance criteria must be locked before execution based on the controlled product specification and the measurement method. Independently of the nominal size claim, calculate particle relaxation time, terminal settling velocity, and Stokes number using the measured distribution and the minimum intended airflow velocity.

Tracer-fidelity acceptance: measured D90 shall not produce a calculated Stokes number greater than 0.1 for the smallest relevant flow time scale selected in the protocol, unless an alternate limit is scientifically justified. The preferred result is substantially below 0.1.

10. Test 3 - Plume Temperature / Thermal Neutrality

10.1 Procedure

1. Measure ambient dry-bulb temperature outside the fog plume.
2. Measure fog/plume temperature at the release plane and at representative downstream distances using a probe arrangement that minimizes evaporative/wetting artifact.
3. Record continuously or at intervals sufficient to capture startup, steady-state, and extended operation.
4. Repeat under the lowest and highest practical ambient relative humidity conditions expected for use if feasible.

10.2 Acceptance

Primary acceptance: no sustained plume rise or fall attributable to a temperature-induced carrier-air density difference may be observed after source momentum has decayed. Provisional engineering target: steady-state plume/ambient temperature difference should remain within ±0.5

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°C at the defined evaluation location, unless comparative drift testing demonstrates that a larger difference does not materially bias the tracer. The final criterion must be approved before execution.

11. Test 4 - Still-Air Vertical Drift

11.1 Procedure

1. Verify background air velocity in the test volume is sufficiently low and stable.
2. Release a controlled fog packet with minimal horizontal/vertical injection momentum.
3. After the predefined initial momentum-decay interval, track the centroid and leading/trailing boundaries against a fixed spatial grid for at least 5 seconds.
4. Perform not fewer than five replicate releases at representative settings.
5. Calculate vertical centroid velocity and compare with the gravitational settling predicted from the measured droplet-size distribution.

11.2 Acceptance

Acceptance: measured sustained vertical drift after the momentum-decay interval shall be consistent with particle-scale settling and shall not show an additional thermally driven plume velocity that is material to the intended airflow study. For a confirmed 4-8 micrometer distribution, a sustained downward centroid velocity materially exceeding approximately 2 mm/s should trigger investigation because it exceeds the calculated settling speed of an 8 micrometer water droplet under representative room conditions.

12. Test 5 - Source Momentum / Outlet Velocity

12.1 Procedure

1. Measure outlet velocity profile for each intended port/hose/wand/fan configuration.
2. Measure centerline velocity decay downstream from the release point.
3. Identify the minimum distance at which release momentum is small relative to the minimum airflow velocity the study intends to visualize.
4. Demonstrate visually that slow tracer introduction does not create an artificial jet, reversal, or eddy in a controlled uniform airflow.

12.2 Acceptance

Acceptance is performance-based: the tracer source must not create or materially alter the airflow feature being evaluated. A provisional quantitative target is that residual source-induced velocity at the observation region be less than 10% of the minimum qualified airflow velocity. If this cannot be met, increase release distance, reduce fan/output, change diffuser/wand geometry, or qualify

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the actual source effect by comparative testing.

13. Test 6 - Comparative Airflow-Tracer Concordance

13.1 Objective

This is the highest-value device-specific test because it answers the practical regulatory question directly: does the CRF6 reveal the same airflow structures as an accepted reference tracer in the same controlled flow field?

13.2 Test matrix

Condition	Flow feature	CRF6 run	Reference-tracer run
Uniform vertical UDAF	Direction and sweep	Required	Required
Obstacle in UDAF	Wake / recirculation	Required	Required
Simulated intervention	Disturbance and recovery	Required	Required
Low-velocity boundary / edge	Reflux / entrainment sensitivity	Required	Required

13.3 Acceptance

Qualitative minimum: both tracers shall identify the same direction of flow and the same presence/absence of predefined critical features (wake, recirculation, reflux, obstruction effect, intervention effect) in all critical regions. Quantitative preferred: if PIV or vector extraction is used, predefine a vector-direction and spatial-correlation criterion before testing (for example, mean angular difference and velocity-field correlation). The laboratory should justify the selected numerical threshold based on method uncertainty and intended use rather than select a threshold after viewing the data.

14. Test 7 - Dynamic Smoke-Study Usability

- Perform representative interventions and operator positioning under dynamic conditions.
- Use slow, deliberate source movement; avoid rapid sweeping of the wand/source.
- Ensure the operator, wand, and camera do not obscure the critical airflow path.
- Demonstrate first-air protection, sweep over/away from exposed product/contact surfaces, potential reflux, eddies, and intervention recovery.
- Retain raw video, not only edited clips.
- Document expected airflow, observed airflow, acceptance/disposition, and any repeat views.

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15. Data Integrity and Raw-Data Requirements

- All raw instrument files, screenshots, environmental data, videos, calibration certificates, and analysis files shall be retained.
- No unsuccessful or anomalous run may be deleted. It must be retained and dispositioned as valid, invalid for a documented technical reason, or a protocol deviation.
- Calculations shall be reproducible from retained raw values.
- Any data transformation, smoothing, image enhancement, or video editing used for presentation shall be documented; original unmodified files shall remain available.
- Protocol changes after execution begins require documented approval and justification.

16. Deviations and Failure Investigation

Any failure to meet a predefined acceptance criterion shall be investigated. The investigation should distinguish among particle-size failure, thermal plume bias, source-momentum bias, environmental instability, measurement-method artifact, configuration error, and study-execution error. Retesting is permitted only after the cause is documented and the corrective action is defined; original results remain part of the record.

17. Final Report Requirements

1. Identify CRF6 serial number and complete tested configuration.
2. Summarize all predefined acceptance criteria and pass/fail status.
3. Report measured frequency, droplet distribution, thermal data, vertical drift, source-velocity results, and comparative tracer outcome.
4. Include calculated relaxation time, terminal settling velocity, and Stokes number based on measured size data.
5. Attach or reference all raw data, calibration records, videos, photos of setup, and deviations.
6. State a narrow conclusion tied to the tested configuration and intended operating envelope.
7. Define requalification/change-control triggers.

18. Proposed Final Qualification Conclusion (Use Only if All Acceptance Criteria Pass)

The tested Applied Physics CRF6 configuration demonstrated a micron-scale aerosol distribution with low calculated particle inertia and gravitational slip, no material thermally induced plume bias, no material source-momentum distortion within the qualified observation region, and concordant visualization of predefined airflow

features relative to the reference tracer. Within the tested operating envelope, the CRF6 is therefore qualified as a passive, functionally neutrally buoyant airflow-visualization tracer for the intended application. This conclusion is limited to the tested configuration and does not replace the facility-specific dynamic smoke-study qualification.

19. Change-Control / Requalification Triggers

- Change in ultrasonic transducer or driver design/revision.
- Change in operating frequency specification.
- Change in fog-output control algorithm or fan hardware.
- Change in outlet, hose ID/length, wand/nozzle, Y-adapter, diffuser, or other flow path.
- Material change in recommended water specification or operating temperature range.
- Field evidence of altered fog behavior, visible settling, unexpected plume rise/fall, or inadequate visualization.
- Regulatory or standards change that materially alters acceptance expectations.

20. References

[1] U.S. FDA. Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice: Guidance for Industry. 2004.

[2] U.S. FDA. Warning Letter: Wizcure Pharmaa Private Limited, MARCS-CMS 726378. June 24, 2026.

[3] U.S. FDA. Warning Letter: International Medication Systems Limited, MARCS-CMS 727560. July 2, 2026.

[4] U.S. FDA. Warning Letter: Sato Pharmaceutical Co., Ltd., MARCS-CMS 723059. May 18, 2026.

[5] Kennedy DA. Water fog as a medium for visualization of airflows. Ann Occup Hyg. 1987;31(2):255-259. doi:10.1093/annhyg/31.2.255.

[6] Lozano A, González-Espinosa A, García JA, Calvo E, Barroso J, Barreras F. High flow-rate ultrasonic seeder. Flow Meas Instrum. 2014;38:62-66. doi:10.1016/j.flowmeasinst.2014.04.002.

[7] Ayati AA, Kolaas J, Jensen A, Johnson GW. A PIV investigation of stratified gas-liquid flow in a horizontal pipe. Int J Multiphase Flow. 2014;61:129-143. doi:10.1016/j.ijmultiphaseflow.2014.01.008.

[8] Auvinen M, Kuula J, Grönholm T, Sühring M, Hellsten A. Physics of Fluids. 2022;34(1):015124. doi:10.1063/5.0076495.

[9] Melling A. Tracer particles and seeding for particle image velocimetry. Meas Sci Technol. 1997;8(12):1406-1416. doi:10.1088/0957-0233/8/12/005.