

## Instructions for use of a Penn-Century MicroSprayer® Aerosolizer - Model IA-1B

U.S. Patent Nos. 5,579,758; 5,594,987; 5,606,789

### ► For doses of 1 ml in Rat, Guinea Pig or Custom lengths



### Precise, hand-operated and air-free

The Penn-Century MicroSprayer® Aerosolizer – Model IA-1B is a unique, patented atomizer that is widely used for precise, pre-clinical intratracheal aerosol administration. When used with a 0.5 ml gas-tight precision glass syringe or 1 ml polycarbonate syringe, it produces a fine, highly concentrated, air-free mist from the end of a small-diameter delivery tube. The Model IA-1B can successfully aerosolize a wide range of pharmaceutical, biologic and toxicologic liquids, solutions and suspensions. It permits precise aerosol drug administration to the lungs, nasal cavities or other *in vivo* and *in vitro* applications, including analysis and testing of safety and efficacy of pulmonary and respiratory drug delivery methods.

The device is made of stainless steel and other chemically resistant components and is sterilizable and reusable. It is available in two standard lengths for intratracheal use in rat or guinea pig, or in any custom length (straight or with bend) for use in larger animals (rabbit, ferret, dog, sheep, cow, monkey, etc.), or for *in vitro* applications.

## Planning for use – What you need to know before you start

The Penn-Century MicroSprayer® Aerosolizer - Model IA-1B is unlike any other hand-held atomizer. It has been designed to permit rapid, precise, efficient pulmonary administration of aerosols. The ability to do this depends entirely on the skill of the user. It takes practice, patience, skill and manual dexterity to use these devices correctly as intended, particularly for intratracheal *in vivo* applications. Because of its unique design, careful attention is also required to maintain it in good working condition.

### 1. Understand how this technology works

The MicroSprayer® Aerosolizer – Model IA-1B is a unique, patented air-free atomizer that works by manual pressure only. There are tiny components in the tip of the device that help generate an aerosol when liquids, solutions or suspensions are pushed through them with sufficient speed and force, using either the 1 ml polycarbonate or .5 ml precision glass syringe provided. These syringes are gas-tight and suitable for the pressure requirements for operation of the MicroSprayer® Aerosolizer – Model IA-1B. Do not substitute another commercial syringe or one of another size without consulting us.

### 2. All air must be eliminated from inside the syringe and MicroSprayer® before use

This atomizer operates with manual pressure only - rather than with compressed air or gas. If there is any air that is trapped inside of the syringe or the tubing of the MicroSprayer® it will cause streaming rather than produce a good uniform aerosol. Users must follow our instructions below for eliminating air from the syringe prior to use.

### 3. The user must practice first with water in the open air

During *in vivo* intratracheal use, the user will not be able to observe the aerosol coming from the MicroSprayer®. Therefore, it is essential to practice use of the device with water in the open air to observe how rapidly the plunger of the syringe must be pushed to produce a uniform puff or plume of aerosol. Any air trapped inside the syringe will also degrade the uniformity of the aerosol. Before *in vivo* use with their own formulation, the user must practice loading the device correctly with water only - to eliminate air and get a feeling for how hard they must push the plunger to produce a uniform aerosol without streaming.

### 4. The MicroSprayer® Aerosolizer must be cleaned fully to avoid blockage

As noted above, the MicroSprayer® Aerosolizer is a unique atomizer. Contrary to appearances, it is not a hollow catheter, cannula or needle. Aerosol is generated when formulations are pushed with sufficient manual pressure through tiny patented components in the tip of the MicroSprayer®. The inner diameter through these components for the Model IA-1B is about 140 microns in diameter. When it is used to administer particle suspensions, additional care must be taken to clean the MicroSprayer® Aerosolizer according to our instructions below to prevent a build-up or agglomeration of suspended particle material in the tip that can block or clog it and interfere with performance.

### 5. The MicroSprayer® Aerosolizer must be handled with care. The MicroSprayer® Aerosolizer is made of narrow, stainless steel tubing. Care must be taken not to manipulate it or force it into a sharp bend or crease, as this will damage it beyond repair.

### 6. Users must test the feasibility of aerosolizing their own formulations prior to experimental use

This technology has been cited in hundreds of peer-reviewed published studies in which it was used successfully to aerosolize a wide range of pharmacologic and biologic materials, including nanoparticles, viral and bacterial agents, liposomes, proteins, peptides and oligonucleotides. In general, many studies have demonstrated that the MicroSprayer® technology does not exert shear stresses on the viability of biologic materials as do systems dependent on compressed air. However it is the responsibility of the user to test their

own formulation with this technology prior to use in an *in vivo* or *in vitro* model. Users are responsible for determining the feasibility of aerosolization of their particular formulation at the dose volume, composition and frequency they wish to use. In particular, researchers must:

- Test the effect upon their own formulation when it is aerosolized with this technology and
- Test their ability to aerosolize the same formula repeatedly in the MicroSprayer® Aerosolizer without clogging (blocking) of the tip.

**7. Users must practice *in vivo* use with imaging agents or dye before use with their formulation**

Even when users have done intubation in past, it is important to plan to practice *in vivo* use of the MicroSprayer® Aerosolizer BEFORE working with your test formulation to confirm that the tip of the MicroSprayer® Aerosolizer was correctly positioned. Was the test formulation well-distributed in the lungs, or was the dose mostly deposited in the trachea or swallowed? Some materials used for validating deposition include: dye, radio-opaque contrast or imaging materials such as Technetium-99m and scintigraphy methods, or fluorescent particles in suspension. If a dye is used, we recommend very dilute solutions only < 1% of laboratory dye, such as Methylene blue or Evans blue, or similar. **(DO NOT use India ink for this purpose, as it may contain carbon particulates or shellac that can clog the sprayer tip over time.)** If the solution is not sufficiently diluted, it can clog the tip of the sprayer. Be sure to flush the device fully after use.

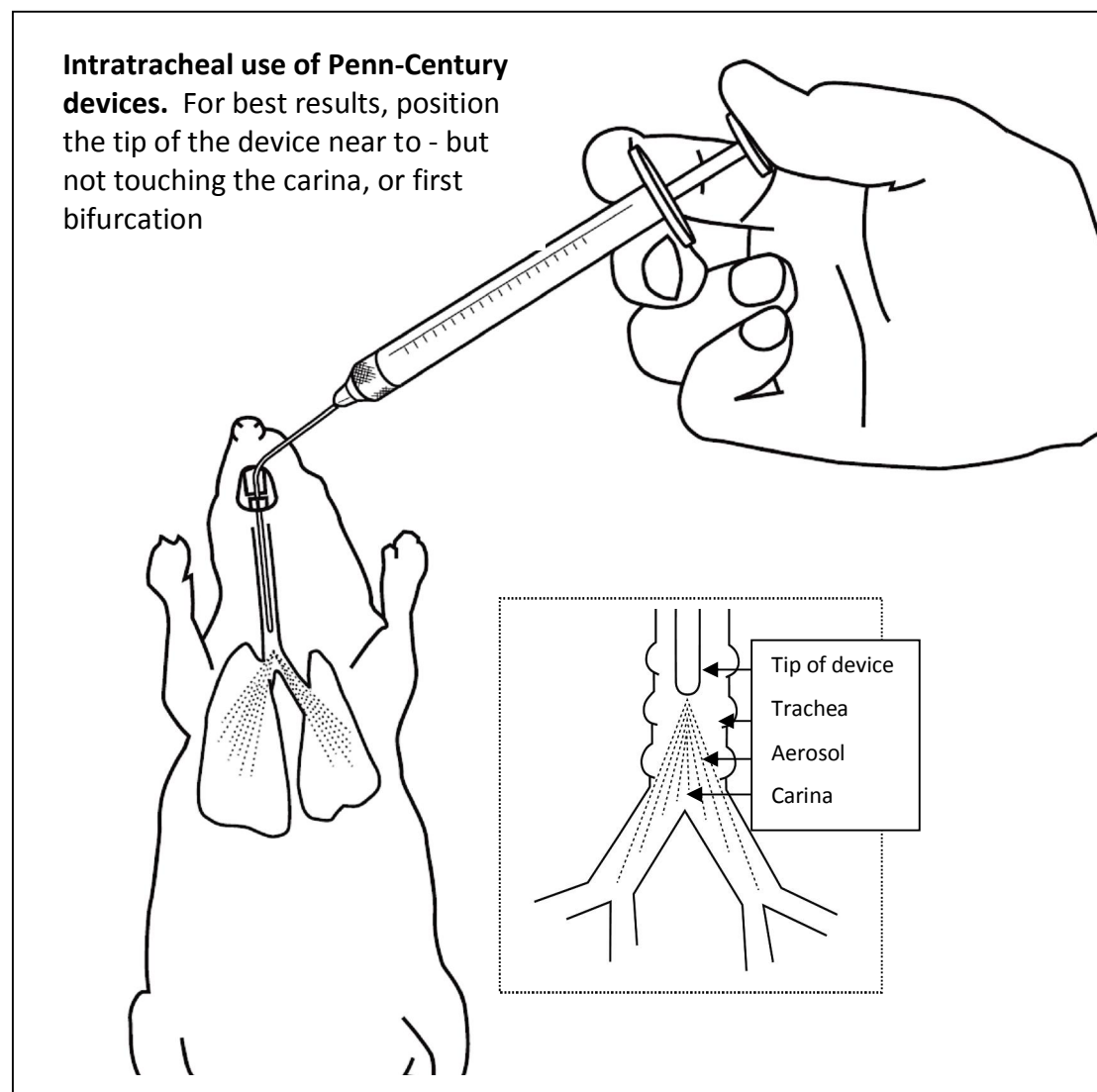
**8. We offer helpful accessories.** Penn-Century also makes several helpful accessories, including a Small Animal Laryngoscope and a Mouse Intubation Platform to help users quickly and easily visualize the epiglottis and insert the tip of the MicroSprayer® Aerosolizer more rapidly, safely and easily for optimal results.

**9. Before starting, users must have a plan how they will determine and measure dose deposition and dose response.** This device has been designed to permit rapid, precise, efficient and safe pulmonary administration of aerosols. The ability to do this depends entirely on the skill of the user. Use of this equipment for intratracheal applications requires understanding of correct intubation and anesthesia techniques in experimental animals. Once the animal has been correctly anesthetized, the user must practice insertion of the MicroSprayer® and operation of the syringe in a manner that will result in consistent, uniform deposition of the aerosol in the lungs – without injury to the animal.

**10. Mastering the variables leads to more reproducible and relevant data.** The use of this intratracheal technology requires mastering many different variables for correct use. Until these variables are mastered and the researcher can operate and maintain the devices consistently as intended, they will have no reliable, reproducible way to distinguish if the data they obtain was the result of their formulation and dose size or was caused by incorrect insertion or care of the equipment. Once the user has mastered the ability to insert and operate the device in a reliable, safe and consistent manner, they must have a plan for how they will determine and quantify dose response and dose deposition in the lungs. As manufacturers, Penn-Century cannot advise users on these methods, but examples can be found in the more than 1,300 scientific publications citing our liquid and dry powder devices.

## CAUTIONS FOR INTRATRACHEAL *IN VIVO* USE

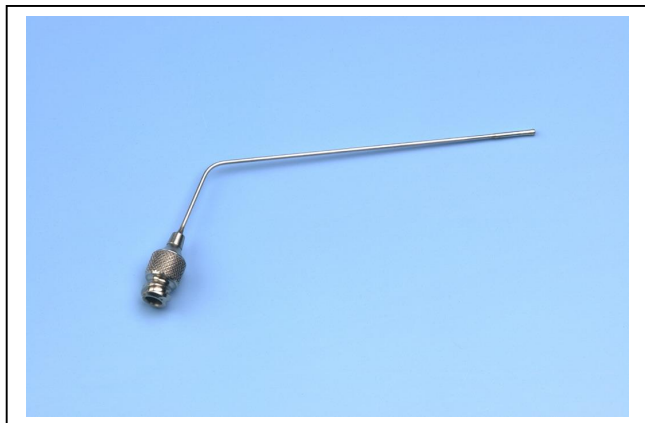
Use of liquid or dry powder Penn-Century devices for intratracheal applications is essentially a form of intubation. Familiarity with intubation and anesthetized animal prep is a prerequisite for use of these devices. Unlike intubation, some hand motion is required for correct use of the device. When using any Penn-Century intratracheal aerosol device – whether liquid or dry powder, the user must push the plunger of the syringe fast and with force to aerosolize the material inside. For optimal lung deposition, the tip of the delivery tube must be positioned near to, but not touching the carina. **Therefore, the user must exercise care and attention to minimize any forward motion of the hand while pushing quickly and firmly on the plunger, to prevent trauma or injury to the animal.**



**Correct placement in the trachea is essential.** For obtaining the best results for intratracheal use, the placement of the very tip of the delivery tube is critical. In published studies, optimal lung deposition from Penn-Century intratracheal aerosol devices is obtained when the very tip is carefully positioned in the trachea so that the very tip is near to but not touching the carina (first bifurcation) of the anesthetized animal. If the tip of the MicroSprayer® Aerosolizer is inserted only halfway down the trachea, it is possible that the aerosol will only impact against the walls of the trachea, turn to large droplets and be coughed or swallowed. If the tip is too close to the carina, injury can result when the plunger is pushed with sufficient force to generate an aerosol.

## KEY FEATURES:

### MicroSprayer® Aerosolizer (liquid) - Model IA-1B



May be operated with either a gas-tight 0.5ml precision glass syringe or a 1ml polycarbonate syringe

- **The Penn-Century MicroSprayer® Aerosolizer is the only commercially available air-free intratracheal aerosol delivery technology.**
- It can be used to administer **precise doses of aerosol** for intratracheal, intranasal or other *in vivo* or *in vitro* applications.
- The devices have been shown to successfully administer **a wide range of pharmaceutical and biologic agents, as well as toxicological, bacterial and viral materials.**
- The MicroSprayer® Aerosolizer can administer **liquids, solutions or particle suspensions**, including nanoparticle and microparticle solutions.
- **The MicroSprayer® Aerosolizer - Model IA-1B is made of rigid 19-gage stainless steel tubing** and other chemically resistant components, and is designed to be sterilized and re-used.
- **Patented components in the tip of the device help to generate an aerosol** when used with the gas-tight syringe provided.
- **The hub of the MicroSprayer® Aerosolizer - Model IA-1B is luer hub.** It can be operated with either a gas-tight 0.5 ml precision glass syringe (sold separately) or a 1 ml polycarbonate syringe (provided). The Model IA-1B operates at 700 pounds per square inch (psi) of manual pressure.
- **Standard lengths of the device are typically made with a 120-degree bend** to permit the user to keep their hand out of the line of sight to the epiglottis.
- **For intratracheal use**, the length of portion that is inserted into the trachea is designed to reach from the incisors to above the carina. For use in rat, the intratracheal portion is 2" after the bend. For use in guinea pig, it is 3" after the bend.
- **Custom lengths are available for straight, longer or shorter applications**, and for insertion into the trachea or into the lung via an endotracheal tube or bronchoscope.
- **Particle size range: Mass Median Diameter of 25-30  $\mu$ m (microns)** **NOTE:** Particles analyzed with water using laser defraction method.
- **The MicroSprayer® Aerosolizer can be safely cleaned with hot water or any organic solvent**, autoclave or ultrasonic cleaner, and most, but not all, disinfectants. It is meant to be sterilized and re-used.

## **SYRINGES FOR USE WITH THE MICROSPRAYER® AEROSOLIZER - MODEL IA-1B**

The MicroSprayer® Aerosolizer Model IA-1B can be operated either with a commercial gas-tight 0.5 ml precision glass syringe (sold separately) or 1 ml polycarbonate syringe (provided). NOTE: These syringes are intended to be filled with ONE DOSE at a time. The plunger must be pushed quickly and with force to produce a uniform aerosol and must be pushed with the same force until the plunger fully empties the syringe.

### **0.5 ml gas-tight precision glass syringe**



- Operates any MicroSprayer® Aerosolizer Model IA-1B
- Maximum capacity: 500 microliters
- Provides optimal aerosol delivery
- Precision glass safety syringe
- Sterilizable with standard methods and organic solvents, including acetone
- Commercial gas-tight syringe with Teflon® plunger tip
- Do not remove plunger all the way when cleaning, per manufacturer's instructions

### **1 ml polycarbonate syringe**

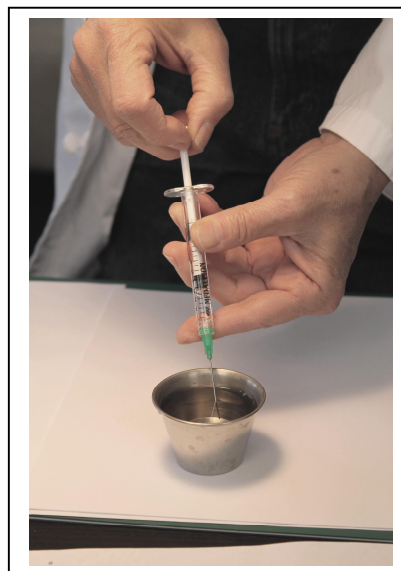


- Operates any MicroSprayer® Aerosolizer Model IA-1B
- Maximum capacity: 1 ml
- May be cleaned with bleach or ethanol
- Commercial gas-tight syringe with Teflon® plunger tip
- For precise aerosol doses up to 1 ml

## Filling the syringe



**Method 1:** Immerse the tip of syringe directly and fill it prior to attaching the MicroSprayer® Aerosolizer



**Method 2:** Attach a standard, blunt dosing needle or a hypodermic needle to the syringe and fill it prior to attaching the MicroSprayer® Aerosolizer

**NEVER fill the syringe through the MicroSprayer® Aerosolizer.** This may cause blockages to occur. It is best to fill the syringe first and then attached the MicroSprayer® Aerosolizer. Depending on the material being used, you may use any of the following methods to fill the syringe:

**Method 1:** Remove the MicroSprayer® Aerosolizer from the syringe and immerse the distal tip of syringe into the solution to be delivered. Draw back on the plunger. Push out any air bubbles as noted below. Attach the MicroSprayer® Aerosolizer.

**Method 2:** If there are concerns about handling hazardous materials or contaminating the test formulation, you may fill the syringe from by attaching a standard a hypodermic or blunt dosing needle to the glass or plastic syringe. This permits filling the syringe from any sterile glass reservoir with a septum, test tube or other source. Once the syringe is filled, push out any air bubbles, as noted below, remove the loading needle and attach the MicroSprayer® Aerosolizer.



### Removing all air bubbles from the syringe

The Penn-Century MicroSprayer® Aerosolizer is an air-free aerosol system. Air bubbles will cause the quality of the spray to degrade. After loading the syringe, turn it with the distal tip pointed upward, tap the sides of the syringe with your fingertips and push the plunger to force any air bubbles out the distal tip. Always push out any air bubbles trapped in the syringe prior to use.

**NEVER FILL the syringe through the MicroSprayer® Aerosolizer as this may cause it to become blocked or clogged.**





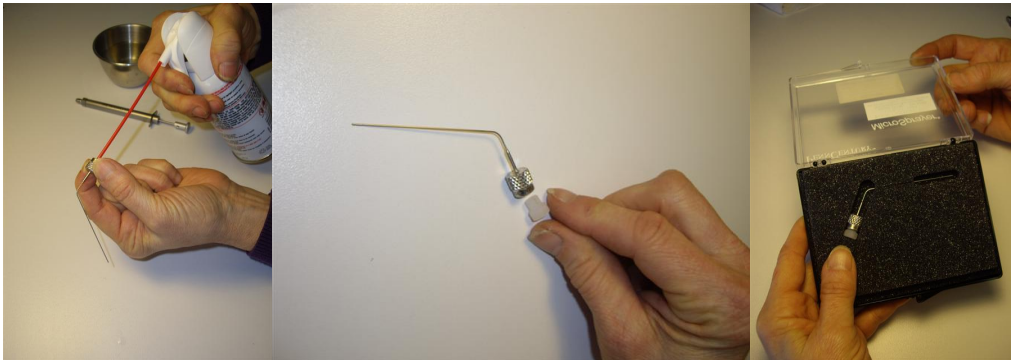
### Determining the optimal dose range for your applications

- Direct aerosol administration to the lungs with a Penn-Century intratracheal device permits far more precise quantification of the delivered dose and far higher drug concentration than is possible with large nebulizer or exposure systems for animals that mix drug with compressed air that is blown - at high momentum - at the nose of the animal. The aerosol from the MicroSprayer® Aerosolizer is gentle, air-free, low momentum, highly concentrated and precisely quantifiable.
- A review of literature citing Penn-Century devices indicates that intratracheal aerosol delivery with our devices permits far more efficient administration of very small doses. They also permit delivery of far larger doses volumes than would be possible by animal nebulization/exposure/ inhalation systems or would be safe if using liquid bolus/droplet instillation through a gavage needle, catheter or endotracheal tube.
- **Researchers should take into consideration that the optimal, most effective dose range they can administer using a Penn-Century intratracheal drug delivery device may be an amount that is far smaller or far larger than is possible within the limitations of standard methods of pulmonary drug delivery in animal models.** The user must conduct feasibility experiments to determine the dose response curve and the optimal dose for their own formulation by increasing the dose in small increments to determine the minimum or maximum effective dose, and to plan for this process in their experimental design.



## Determining deposition

- Use of all Penn-Century devices for intratracheal applications is essentially a form of intubation. The user must insert the tip of the device gently down the trachea of the anesthetized animal, near to but not touching the carina. Particularly when working with small animals, some users may wish to practice on several test animals by spraying with dye or a fluorescent or radio-opaque contrast agent to determine if the tip of the MicroSprayer® Aerosolizer was correctly positioned, and to determine if the test liquid was well-distributed in the lungs, or was mostly deposited in the trachea or swallowed or wound up in the esophagus.
- Some users have used radio-opaque materials such as Technetium-99m and scintigraphy methods. If a dye is used, we recommend a 1% solution of laboratory dye, such as Methylene blue dye or Evans blue dye. (We strongly discourage using India ink for this purpose, as it may contain carbon particulates or shellac that can clog the sprayer tip over time.) If the solution is not sufficient diluted, it can clog the tip of the sprayer. Be sure to flush the device fully after use.
- Penn-Century also makes several helpful accessories, including a Small Animal Laryngoscope and a Mouse Intubation Platform to help users quickly and easily visualize the epiglottis and correctly insert the tip of the MicroSprayer® Aerosolizer for optimal results.



*Clean and test the MicroSprayer® Aerosolizer with filtered or distilled water after use. Then apply compressed air to expel any remaining liquid. Attach the protective caps and return to original boxes for storing.*

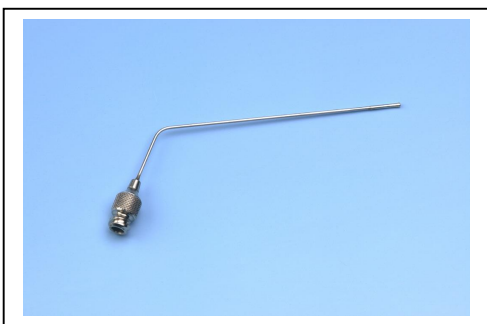
## Care of MicroSprayer® Aerosolizer

**The MicroSprayer® Aerosolizer must be cleaned immediately and thoroughly after use to maintain it in good working condition.** It consists of stainless steel and other chemically resistant components and can be subjected to any standard sterilization or autoclaving procedure: gas, liquid, wet, dry, heat, cold, *dilute* acids, *dilute* bases, etc. In addition, the MicroSprayer® Aerosolizer can be heated as high as 500 degrees Fahrenheit. To avoid damage to the device, if you are uncertain about use of a particular method or material, PLEASE CONTACT US FIRST.

It is essential to fully clean, test, dry and properly store your device after use to insure that it performs as it should. Solutions and suspensions used in the device are forced under pressure through patented atomizing components at the tip of the MicroSprayer® Aerosolizer. Over time, if the device is not fully flushed out and cleaned after use, there may be a build-up of residual material that hardens and clogs the tip.

- **To minimize clogging, solutions should be filtered before spraying.** In addition, reasonable care should be taken to avoid dust and dirt which can foul the sprayer tip. For instance, when placing the assembled system or individual components on a surface, it is best to avoid surfaces from which the device might pick up dirt or lint. A large, clean Petri dish works well for this purpose.
- **ALWAYS clean and fully flush the MicroSprayer® Aerosolizer after use** with very hot distilled or filtered water. You may also use any organic solvent, such as ethanol, methanol, chloroform, xylene or acetone to dissolve any materials that may be inside. The following are also safe for cleaning and disinfecting the device: Cidex®, Cidex Plus®, Cidex OPA®, Enzol® Solutions. If you wish, you can soak the devices in any of these as well, to soften any material that has become hardened in it, and then flush it out with the same solution using the syringe. You may fill the syringe with solvent and spray it into an enclosed container. (ALWAYS USE CAUTION WHEN SPRAYING ANY SOLVENT OR HAZARDOUS CLEANING AGENT TO FOLLOW SAFETY INFORMATION PROVIDED AND AVOID CONTACT OF THE SPRAYE WITH EYES, FACE OR SKIN.
- **Never use a flame or high heat to clean the MicroSprayer® Aerosolizer – as this may damage it beyond repair.**
- **Do not subject the MicroSprayer® Aerosolizer to extreme changes of temperature.**
- **Is best to avoid cleaning the device with undiluted acid or base solutions, or bleach (Clorox™ /Clidox™), as these can be corrosive.**
- The MicroSprayer® Aerosolizer may also be cleaned with ultrasound (sonicated) or autoclaved at standard sterilization temperatures.
- **ALWAYS test the MicroSprayer® Aerosolizer with water after cleaning it** and before storing it to observe that it continues to deliver a full, uniform plume of spray that is as good as its operation when new.
- **ALWAYS blow air through the MicroSprayer® Aerosolizer fully before storing to eliminate remaining liquid inside.** Direct a small stream of compressed air into the threaded sprayer hub of the MicroSprayer® Aerosolizer until all fluid remaining in the sprayer tip is expelled. Products such as "DUST-OFF" or similar for cleaning computer keyboards are also suitable. Do not blow compressed air through the device without testing it first with water. If it is partly clogged, drying it with air will may further harden any material in the tip.
- **ALWAYS clean the protective plastic end cap** that came with the MicroSprayer® Aerosolizer and screw it back on before storing it to remove any dust or grit that has gotten on it Always store the MicroSprayer® Aerosolizer and FMJ-250 Syringe in the original boxes in which they were shipped to prevent it from getting dropped or bent.

## What to do if MicroSprayer® Aerosolizer becomes blocked or clogged



If the MicroSprayer® tip starts to become partially blocked, you will notice an increase in the force required to depress the syringe plunger. IF SO, STOP PUSHING!

In general, it does not help at this point to increase the force on the plunger as this may only serve to further drive the offending material into the small passages of the sprayer tip or cause damage to the plunger or syringe. If this occurs:

1. Remove the MicroSprayer® Aerosolizer and soak it in very hot, boiled dionized or distilled or filtered water, or soak in organic solvent and draw back on the syringe plunger, holding it in the fully retracted position for 15 seconds.
2. Reattach the MicroSprayer® Aerosolizer to the syringe. With the tip of the MicroSprayer® Aerosolizer in very hot water or organic solvent, attempt to pull back on the plunger of the syringe. Then remove the MicroSprayer® Aerosolizer, eject the contents of the syringe and flush it thoroughly with water. Repeat.
3. It is perfectly safe to clean the device with stronger organic solvents (It is safe to push through any organic solvent - methanol, ethanol, even acetone, chloroform, Trichloroethylene).
4. **NEVER** insert a pin or needle into the hole at the tip of the MicroSprayer® Aerosolizer to clear it. This could crack or damage the aerosolizing components.
5. **USE CAUTION when using ultrasound cleaners with the MicroSprayer® Aerosolizer.** It is possible to immerse the MicroSprayer® Aerosolizer in an ultrasound with water or solvent to try to remove blocked material. AVOID placing the tip of the MicroSprayer® Aerosolizer directly on the bottom surface of the ultrasound as the vibration may alter or damage the components in the tip. We do not know if repeated use of ultrasound will affect the device. This should be used as a last resort only.
6. The following method has been successful for some users: SDS (sodium dodecyl sulfate) 5% NaHO (NaOH Sodium hydroxide) 2%; then Ultrasound; then Autoclave.
7. If that doesn't work, and the MicroSprayer® Aerosolizer is completely blocked and is not letting any liquid pass through at all, contact Penn-Century, Inc. for additional recommendations.
8. Recently, Penn-Century has introduced a new tool for unblocking the tip of the MicroSprayer® Aerosolizer Model IA-1B that uses the pressure of the syringe to push solvent or hot water in reverse from the tip to hub of the sprayer. Contact us for details about this "Reverse Cleaning Adapter."

*For a full summary of the company's repair and warranty policies, please review the Penn-Century Terms and Conditions.*

**As manufacturers, Penn-Century, Inc. can offer:**

- Product knowledge
- Operation of our devices
- Familiarity with published studies related to use of the same device and, if possible, similar drugs
- Familiarity with customer feedback about them

*These instructions and photos are the property of the Penn-Century, Inc. They must be not be reproduced without the written consent of Penn-Century, Inc.*

**IMPORTANT NOTICE: Requirements for citing use of Penn-Century devices in publications, abstracts and presentations**

As a condition of sale, the Buyer agrees that upon publication or presentation of any research conducted using a Product, the Penn-Century name as the manufacturer ("Penn-Century, Inc. Wyndmoor, PA") and the name of the Products must be correctly spelled and cited, and include Penn-Century's registered trademark and model number as follows and as applicable: "MicroSprayer®Aerosolizer – Model \_\_\_\_", "FMJ-250 High Pressure Syringe", "Dry Powder Insufflator™ - Model \_\_\_\_" or "Small Animal Laryngoscope – Model LS-2". A breach of this section shall result in immediate harm to Penn-Century, and in addition to any and all rights available to Penn-Century, Penn-Century shall be entitled to an injunction or other equitable relief as a remedy for such breach.

For any questions, contact us at Penn-Century, Inc. – [info@penncentury.com](mailto:info@penncentury.com) or 215-753-6540.

*Rev. 23May2013*