A Comparison of Inline MDI Actuators for Delivery of a Beta Agonist and a Corticosteroid with a Mechanically Ventilated Lung Model

Joseph L Rau PhD RRT, Crystal L Dunlevy EdD RRT, and Richard L Hill

INTRODUCTION: The type of metered dose inhaler (MDI) actuator/adaptor as well as the type of drug used may influence the dose of drug delivered to intubated, ventilated subjects. PURPOSE: The purpose of this study was to evaluate MDI aerosol drug delivery of albuterol (Proventil™) and flunisolide (AeroBid™) through an endotracheal tube (ETT) using a novel bidirectional nonreservoir actuator, the Allegiance Healthcare Corp Airlife MiniSpacer (MiniSpacer) in comparison with four other MDI actuator/reservoir devices. METHODS: The MiniSpacer was compared to the DHD Healthcare Aerosol Cloud Enhancer (ACE), the Allegiance Healthcare Corp Airlife MediSpacer (MediSpacer), the Monaghan Medical Corp AeroVent (AeroVent), and the Hudson RCI® Inline MDI Adaptor (Hudson Inline) for MDI administration of albuterol and flunisolide, using a mechanically ventilated lung model. Drug dose was collected at the end of the ETT on a filter and was analyzed by spectrophotometer. Drug delivery at the end of the ETT is expressed as a percent of the dose measured from the MDI. RESULTS: Mean (standard deviation) doses of albuterol were: Hudson Inline—12.8% (6.9), MiniSpacer—17.2% (1.2), AeroVent—17.7% (2.5), ACE—30.0% (2.0), and MediSpacer—31.8% (1.6). Mean (standard deviation) doses of flunisolide were: Hudson Inline—5.0% (0.9), AeroVent—11.4% (1.8), ACE—12.4% (2.8), MediSpacer—13.1% (2.2) and MediSpacer—21.0% (1.8). There were significant differences across device types (p < 0.005), for both albuterol and flunisolide delivery by one-way analysis of variance (ANOVA). CONCLUSION: The new nonreservoir bidirectional MDI adaptor (MiniSpacer) was superior to the unidirectional Hudson nonreservoir actuator in dose delivery through an ETT for both albuterol and flunisolide. For delivery of albuterol, the bidirectional adaptor was equivalent to the AeroVent reservoir but not as efficient as the MediSpacer or ACE reservoirs. For delivery of flunisolide, the bidirectional adaptor was equivalent to both the ACE and the AeroVent, but lower than the MediSpacer. Delivery of the corticosteroid flunisolide was lower for all devices compared to albuterol. [Respir Care 1998;43(9):705–712] Key words: Aerosol delivery, inline MDI activators, lung models, mechanical ventilation, metered dose inhalers, spacer devices.
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Fig. 1. Equipment configuration for in vitro lung model testing of reservoir and nonreservoir MDI actuating devices for inline ventilator delivery.

Patient Y, delivered a greater volume of aerosol bronchodilator drug particles in the 1–5 μm size range than the elbow type of adaptor, but less volume compared to a reservoir device (the Monaghan AeroChamber inline spacer*). The in vivo study by Fuller et al reported that an inline T-type device delivered less bronchodilator drug to the lungs than either reservoir devices of varying volume or an elbow type of adaptor. The T-type adaptor is often referred to as an inline nonchamber, or nonreservoir, device. The nonreservoir inline MDI adapters have minimal volume compared to reservoir devices, and this may account for the lower drug delivery with the T-type devices.* The type of MDI drug used, such as β2 agonist or corticosteroid, has also been shown by Ahrens et al to affect the delivery performance of reservoir devices. This variation may affect performance of nonreservoir inline T-type adaptors as well, and has not been evaluated in the literature.

Recently a novel inline, nonreservoir type of MDI actuator has been developed by Thayer Medical Inc, and marketed by Allegiance Healthcare Inc, which offers a bidirectional aerosol spray when placed inline in the inspiratory limb of a ventilator breathing circuit. This design theoretically offers a greater holding volume for the aerosol, compared to the unidirectional spray from previous inline nonreservoir actuators. The increased volume for the aerosol spray plume may improve drug delivery for this type of nonreservoir device. The purpose of this study was to evaluate dose delivery of an MDI bronchodilator and corticosteroid drug through an ETT with the nonreservoir bidirectional adaptor compared to 3 available reservoir devices and a unidirectional inline nonreservoir device, using a mechanically-ventilated adult lung model.

Materials and Methods

Lung Model A Puritan Bennett Model MA-1 (MA-1) provided positive pressure breaths to a dual-chambered test lung, with Compliance setting = 50 mL/cm H₂O, and Resistance set by the 8.0 mm tubing of the test lung, using a disposable adult ventilator circuit (Dart Respiratory, Uniset). The MA-1 volume setting was adjusted to achieve a delivered volume of approximately 800 mL to the test lung at a respiratory rate = 10/min and flow = 60 L/min. Use of the lung simulator provided both an inspiratory and expiratory phase during drug dose measures. Volume, inspiratory flow, and respiratory rate were verified prior to dose measure, using the BioTek adult ventilator tester, Model VT-1. The test lung and the expiratory limb of the ventilator circuit were isolated using a high efficiency particulate air (HEPA) filter to prevent aerosol drug contamination of the lung or environment. A servo-controlled Fisher & Paykel heated humidifier (Model MR 480) was used to provide approximate saturation of inspired gas between 30–35°C, as measured at the circuit Y-piece. A right angle adaptor connected the circuit Y-piece to an 8.0 mm inner diameter ETT. Aerosol drug was collected on a filter between the end of the ETT and the test lung. The distal tip of the ETT was inserted through a 15 mm adaptor and the cuff inflated. The adaptor was inserted into the larger 22 mm port of the collecting filter, with the Murphy eye and tip projecting into the filter housing but not touch-
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Fig. 2. Diagram of reservoir and nonreservoir MDI actuating devices for inline ventilator delivery, giving dimensions of each device and direction of aerosol drug spray. Device illustrations are not to scale with respect to each other.

ing the filter material. A diagram of the configuration is shown in Figure 1. The ETT was oriented horizontally to prevent condensation and wash-through of aerosol drug to the collecting filter, and the natural curve of the ETT was preserved during dose delivery. The predictive validity of in vitro bench tests of aerosol delivery has been established by Fuller et al and by O’Riordan et al.6–7 In their studies, in vitro results generally gave higher absolute amounts of drug delivery compared to in vivo, but proportional differences between devices or delivery methods remain accurate.

The bidirectional actuator/adaptor T (MiniSpacer) was compared with four other brands of MDI actuator/adaptor: the DHD Healthcare Inc Aerosol Cloud Enhancer (ACE), the Allegiance Healthcare Corp Airlife MediSpacer (MediSpacer), the Monaghan Medical Corp AeroVent (AeroVent), and the Hudson RCI® Inline MDI Adaptor (Hudson Inline). Diagrams of the five MDI adapters are shown in Figure 2. Assembly of reservoirs and actuator/adaptors followed manufacturers’ specifications. The ACE, AeroVent and MediSpacer reservoirs were placed on the inspiratory limb of the ventilator circuit, just proximal to the Y-piece. The ACE was placed in a reverse-firing position, and the MediSpacer and AeroVent reservoirs in a forward-firing position. Both the Hudson Inline adaptor and the MiniSpacer were placed in the inspiratory limb of the ventilator circuit, 22 cm upstream from the Y-piece, to allow comparison with the in vivo study of an inline nonreservoir device as reported in Fuller et al.3

Study Design Using a separate MDI of the drug being tested, 5 actuations of albuterol (Proventil®) or of flunisolide (AeroBid®), respectively, were discharged initially through each device to be tested, and then the reservoir/adaptor washed and dried prior to any test dose measures. This was intended to remove or lessen any electrostatic charge which may affect the dose delivery measures on new and unused devices.8–9

The same MDI canister and ETT were used for dose measurement for each sample set of the 5 different brands of MDI actuating devices, to minimize dose variability due to different MDIs or tubes. Between each dose measurement with a brand in a sample set, the ETT and connectors were rinsed with distilled water and dried. A new MDI canister and ETT were assigned to each set of 5 brands. A total of 6 different MDIs were used for each drug tested, one for each sample set of 5 brands of actuating device. No MDI canister used for dose measures exceeded 50% exhaustion, to further ensure accurate doses. Full MDI canisters were obtained for the trials and weighed to verify
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equivalent fullness. Each new canister had 5 actuations discharged prior to its first use for dose measures. Canisters were shaken prior to use; one actuation was discharged to prime the valve if the canister had not been used in the preceding 4 hours. The ventilator circuit and each MDI actuator device were allowed to warm up and stabilize at the desired temperature range of 30–35°C.

The dose from each of the 6 MDIs used for testing was measured separately. The mouthpiece/actuator of the MDI was attached directly to the collecting filter, which was connected to a vacuum pump operated at a constant 30 L/min. For albuterol, a total of 5 actuations were delivered to the filter, with 30-second intervals and shaking between actuations. The MDI dose of flunisolide was similarly measured, using 3 actuations.

For measurement of albuterol delivery through the ETT, 12 MDI actuations were used to provide an adequate amount of drug on the filter for accurate dose measurement. The nominal dose of albuterol with each actuation is 100 μg from the canister valve. Similarly, for testing of flunisolide delivery, 5 MDI actuations were used to provide adequate drug on the filter for measurement. The nominal dose of flunisolide is 250 μg from the valve per MDI actuation. Drug amounts collected at the end of the ETT were then expressed as dose per actuation, as a percent of the previously measured MDI dose. The order was rotated in which each of the 5 brands was tested. Six samples of each of the 5 brands were tested, with both albuterol and flunisolide. Separate sets of the 6 samples were used for the 2 different drugs tested.

All MDI actuations with the actuators tested were synchronized with the beginning of inspiration, following the manufacturers’ instructions. For the MediSpacer and the inline nonreservoir MiniSpacer, MDI actuation coincided with a manually triggered inspiration, using a simple count rhythm. For the ACE and AeroVent, MDI actuation preceded a manually triggered inspiration by approximately 1 second, using the same count rhythm. Since no instructions were given with the Hudson actuator for the timing of MDI actuation and inspiration, the MDI actuation coincided with the manually triggered inspiration as with the MediSpacer and MiniSpacer. Following each MDI actuation, the ventilator delivered 4 more breaths at the rate of 10/min, to give a total of 30 seconds between each MDI actuation for valve refill. The MDI was shaken between each of the individual actuations. Actuation intervals of 30 seconds, with shaking between actuations, did not affect MDI total or respirable dose (defined as < 6.8 μm) in Everard et al’s study. The same operator activated all MDI doses to minimize inter-operator variability. The ACE, MediSpacer, and AeroVent devices were held horizontally, with the MDI in a vertical position. Both of the inline nonreservoir devices were held manually, with the 22 cm of large-bore tubing connecting to the patient Y main-
tained in a horizontal, approximately straight position. Inspiratory tubing upstream of the nonreservoir device was allowed to droop naturally.

Measurement of Drug All drug measures were performed by spectrophotometric assay, with a Beckman DU 640 spectrophotometer. Accuracy of wavelength was verified prior to measures using a holmium oxide filter with known wavelength pattern of absorbances. The spectrophotometer was calibrated to a baseline zero using solvent with no drug. Prior to each testing session, a standard premixed solution of either albuterol or flunisolide was sampled and the absorbance verified to determine reliability of measures. Following drug collection with albuterol, the collecting filter was washed with 20 mL of an aqueous solution of 0.4 M KH₂PO₄ (potassium phosphate, monobasic) and 0.2 M HCl (hydrochloric acid) for approximately 2 minutes with mild agitation, to dissolve the drug. Preliminary trials verified that additional drug was not recovered with a longer wash time. The sample solution was drawn up from the filter with a glass syringe, and absorbance measured at a wavelength of 276 nm. Drug concentration was calculated by linear regression fitted to serial dilutions of known albuterol concentrations with previously measured absorbances. Drug concentrations as dilute as 1 μg/mL produced absorbance readings in the second decimal place. The drug concentration was calculated for 20 mL of total solution, and averaged as a per actuation dose. Measurement of flunisolide collected at the end of the ETT was the same as for albuterol, except for the use of ethanol as a solvent. The sample solution was measured at a wavelength of 240 nm. The drug assay allowed detection of drug concentrations as low as 0.5 to 1.0 μg/mL.

Data Analysis Descriptive statistics provide the mean, standard deviation and a 95% confidence interval (CI) for dose delivery by each device. Statistical comparisons among the 5 devices for dose delivery were performed by both a nonparametric Kruskal-Wallis analysis of variance (ANOVA), as well as by a parametric one-way ANOVA, since sample sizes were small (n = 6, for each device).

Results

Temperature of the inspired gas in the lung model for albuterol delivery averaged 34.0°C (SD = 0.35). Table 1 gives summary statistics for the amount of albuterol delivered to the filter at the end of the ETT, expressed as a percent of the dose measured from the MDI used, for each type of MDI actuating device tested. The average MDI dose measured for albuterol from the 6 MDIs used was 87.0 ± 3.0 μg.
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Table 1. Summary of dose delivery for albuterol and flunisolide at the end of the ETT for each device, expressed as a percent of the measured MDI dose. For each drug, devices are listed in order of drug delivery amount, least to greatest; devices with the same superscript (*, †, ‡) did not differ significantly from each other in dose delivery. SD = standard deviation; CI = confidence interval; n = 6 each brand.

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<th>Albuterol:</th>
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<td>Hudson Inline*</td>
<td>MiniSpacer†</td>
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<td>Mean (SD)</td>
<td>12.0% (0.9)</td>
<td>17.2% (1.2)</td>
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<td>95% CI</td>
<td>11.1–13.0%</td>
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Analysis of variance was performed, using a significance level of 0.05 to detect differences. Both the non-parametric Kruskal-Wallis, and one-way ANOVA indicated a significant difference across brands (p < 0.005) for delivery of albuterol. Follow-up comparisons using the Scheffé test showed a significant difference (p < 0.05) between brands with different symbols in superscript (*, †, ‡), as shown in Table 1. The bidirectional MDI adaptor (MiniSpacer) delivered a larger average dose of albuterol compared to the Hudson Inline adaptor, and was equivalent to the Monaghan AeroVent, but not as efficient as the DHD ACE or the Allegiance MediSpacer.

The level of extractables from the collecting filter with the aqueous solvent was measured at 276 nm using 20 mL of solvent in a sample of filters with no drug or other substance present. The average (SD) of absorbances measured in this way with 4 filter samples was 0.0098 (0.003). For the Hudson Inline adaptor with absorbance measures that averaged 0.1259, the average noise ratio was 7.8%. The noise level with ethanol and the collecting filter was higher than that seen with the aqueous solvent.

Discussion

Inline nonreservoir, or T-type MDI adaptors, attach to the corrugated tubing of the inspiratory limb of the ventilator circuit. This type of MDI adaptor uses the inspiratory tubing as a reservoir for the aerosol plume, since there is negligible internal holding volume to the adaptor itself. This design offers several advantages: no water or fluid accumulation, minimal weight on the circuit and ETT, and no need to open the ventilator circuit for continual insertion/removal. Due to the relatively small internal diameter of the corrugated inspiratory tubing, high inertial impaction loss could be expected, and this may be the primary mechanism for the lower aerosol delivery seen with inline nonreservoir devices. The design of the MiniSpacer provides a bidirectional spray. The aerosol released from the MDI is divided, with approximately equal portions directed into the inspiratory tubing toward the patient as well as upstream toward the ventilator. As a result of this bidirectional design, the MiniSpacer effectively doubles the holding volume for the aerosol plume. The same amount of aerosol is now contained in twice the amount of inspiratory tubing. In theory, the loss due to inertial impaction would be expected to decline, with a corresponding increase in drug delivery. The results obtained for both albuterol and for flunisolide delivery with the bidirectional MDI adaptor (MiniSpacer) supported this theoretical prediction: drug delivery increased compared to the unidirectional Hudson Inline MDI adaptor, from 12% to 17%, and from 5% to 13%, respectively, for the 2 drugs. For albuterol, the bidirectional inline adaptor delivered doses to the
end of the ETT that were equivalent to the AeroVent (approximately 17% of the MDI dose), but that were lower than the dose seen with the ACE or the MediSpacer, both of which delivered approximately 30% of the MDI dose. With flunisolide delivery, the bidirectional aerosol spray is consistent with results previously obtained by Morén.11 Morén measured the loss of terbutaline sulfate in actuator tubes of various lengths and diameters, as well as in a pear-shaped reservoir device. As the tube diameter increased from 24 mm to 32 mm, loss of aerosol drug decreased. The large pear-shaped reservoir, which was 250 mm in length and 130 mm in diameter at its widest point, gave the lowest aerosol loss, as would be expected. In comparison, the outside diameter of both of the inline nonreservoir devices tested in the present study were 22 mm. Morén’s results support the theory that increased holding volume can reduce aerosol loss, which may be a function of inertial impaction. We suspect that this is the basis for the greater efficiency seen with the ACE and MediSpacer in the delivery of albuterol. The ACE and the MediSpacer have the greatest length and internal diameter of the 3 reservoir devices, which should theoretically minimize internal inertial impaction of the aerosol plume. This is proportionally similar to Morén’s dose measures with the pear-shaped reservoir.

The results of the present study, which showed the lowest aerosol drug delivery for albuterol with the unidirectional inline nonreservoir device (Hudson Inline adaptor), are consistent with results obtained by both Fuller et al, as well as by Bishop et al. Fuller et al found that an inline nonreservoir device (the Instrumentation Industries T-type device, model not specified) delivered less drug to the lungs in vivo, than either a 700 mL or a 167 mL reservoir device.3 The bench study by Bishop et al similarly found that an inline nonreservoir device, the Instrumentation Industries RTC-22, delivered a lower volume of particles < 5.0 μm, as well as a lower percentage of MDI dose, compared to a Monaghan AeroChamber Inline spacer.1 The 2 studies differed on the dose comparison between the inline nonreservoir device and a right-angle MDI adaptor placed directly on the ETT. However, this may have been due to differences in the studies, such as the placement of the inline device, use of humidified gas in Fuller’s study, and in vivo versus in vitro conditions in the two studies.

In vitro delivery of albuterol with the AeroVent reservoir device, using a model of mechanical ventilation, has been reported by several investigators. Fink et al reported that 16.9% ± 2.0% of the dose of MDI albuterol was delivered through an ETT to filters on artificial “bronchi,” with an AeroVent placed on the inspiratory limb proximal to the patient Y, with humidified inspiratory gas.12 A study by Diot et al comparing the AeroVent to the Marquest MDI adaptor showed that 15.4% ± 0.2 of the nominal dose of MDI albuterol was delivered to a filter at the end of the ETT, using a model of mechanical ventilation with humidity.13 In the study by Diot et al, the AeroVent was placed 20 cm above the Y-piece on the inspiratory limb. Both of these amounts agree closely with the 17.7% ± 2.5% for albuterol delivery with the AeroVent in our study. This degree of consistency for the AeroVent device with the previous two studies serves to corroborate the validity of the present results.

A significant result of the present study is the difference in efficiency of the same device, when delivering the β2 agonist albuterol, and the corticosteroid flunisolide. This difference of delivery efficiency with different types of drugs has been reported in the 1995 study by Ahrens et al.5 In general, we found that each device measured delivered a lower percentage of MDI dose with the corticosteroid flunisolide, compared to the β2 agonist albuterol. The average dose of flunisolide across all the devices was approximately 12.6% of the MDI dose compared to 21.7% for albuterol. The percentage of albuterol MDI dose delivered at the end of the ETT ranged from 12%-32%, whereas the percentage of flunisolide MDI dose was 5%-21%, for the various devices in our study (Table 1). This represents a decrease in dose delivery for flunisolide compared to albuterol from approximately 30% to over 50%. Results of our study cannot be compared directly to those of Ahrens et al. Ahrens et al measured delivered dose from 4 brands of reservoirs using cascade impaction testing in contrast to our use of a lung model, with a biphasic breathing cycle, an ETT, humidity, and different flowrates during our inspiratory phase when drug was collected on the filter. The ACE was the only reservoir common to both studies. Despite these differences, Ahrens et al’s study similarly found that with the ACE, the dose of flunisolide collected in the impactor (both throat and stages) was 17% of the total MDI dose, whereas the dose of albuterol collected was 41% of the MDI dose. This represents a 59% decrease in MDI dose delivery for flunisolide compared to albuterol. In our study, the ACE delivered 30% of the MDI dose of albuterol, but only 13.1% of the dose of flunisolide, a 56% decrease in efficiency similar to that seen by Ahrens and colleagues. Reasons for the difference in delivery efficiency for the β agonist compared to the corticosteroid are debated. A common explanation put forth is that the nozzle of the MDI canister differs in diameter between the two drugs albuterol and flunisolide. However, the actuator nozzle receptacle in both reservoir and non-reservoir MDI inline devices is universal for drug canis-
ters. It is hypothesized that the MDI canister nozzles of different drugs will not fit exactly the same into the integral actuator receptacle, and that this may affect the particle size distribution, the respirable mass (commonly defined as particles < 4.7 μm for the Andersen cascade impactor) and the total drug mass delivered with different drugs. The influence of nozzle fit into the integral actuator on drug delivery would be in addition to that of the actuator geometry. The formulations of Proventil® brand of albuterol and AeroBid® brand of flunisolide differ to some extent as well. Both MDI formulations are microcrystalline suspensions. Proventil® is formulated with propellants trichloromono-fluoromethane and dichlorodifluoromethane, along with oleic acid as a dispersing agent. AeroBid® incorporates the same propellants as listed for Proventil® with the addition of dichlorotetrafluoroethane, and a different dispersing agent, sorbitan trioleate. Regardless of the cause(s), it is important to be aware that in vitro testing with various methodologies shows a difference in drug delivery efficiency for devices with integral actuators, when using different types of drugs. All inline MDI actuators for ventilator use currently employ integral actuators.

The in vitro results reported here support the need for an in vivo, clinical comparison of different inline MDI actuating devices, both reservoir and nonreservoir, that are commonly available for aerosol delivery with mechanical ventilation. While significant dose delivery differences are seen in bench testing, it remains to be determined whether these differences will produce significantly different clinical responses to albuterol. Detecting differences in clinical response to a corticosteroid such as flunisolide is more difficult and subject to confounding factors.

**Conclusion**

The new nonreservoir bidirectional MDI adaptor was superior to the unidirectional Hudson nonreservoir adaptor in dose delivery through an ETT for both albuterol and flunisolide. For delivery of albuterol, the bidirectional adaptor was equivalent to the AeroVent reservoir but not as efficient as the MediSpacer or ACE reservoirs. For delivery of flunisolide, the bidirectional adaptor was equivalent to both the ACE and the AeroVent, but lower than the MediSpacer. Delivery of the corticosteroid flunisolide was lower for all devices compared to delivery of albuterol.

**PRODUCT SOURCES**

**Ventilator**

Model MA-1, Nellcor Puritan Bennett Corp. Pleasanton CA

**Test Lung**

Dual adult training/test lung. Model 1600, Michigan Instruments Grand Rapids MI

**Ventilator Tester**

Bio-Tek adult ventilator tester, Model VT-1, Bio-Tek Instruments Inc, Winooski VT

**Humidifier**

Model MR 480, Fisher & Paykel Healthcare Inc, Laguna Hills CA

**Spectrophotometer**

Model DU 640, Beckman Instruments, Fullerton CA

**Drug Collection Filter**

two-way nonconductive anesthesia filter, model 43410-241, Baxter Healthcare Corp, Valencia CA.

**HEPA filter**

Model BB-50T, Pall Corp, East Hills NY

**MDI Actuating Devices**

Aerosol Cloud Enhancer (ACE)

DHD Healthcare, Canastota NY

AeroVent

Monaghan Medical Corp, Plattsburgh NY

Inline MDI Adaptor

Hudson RC1®, Temecula CA

Airlife MediSpacer and Airlife MiniSpacer

Allegiance Healthcare Corp, McGaw Park IL

**Metered Dose Inhaler Drugs**

albuterol (Proventil®)

Schering-Plough Corp, Kenilworth NJ

flunisolide (AeroBid®)

Forest Pharmaceuticals Inc, St Louis MO

**Ventilator Circuit**

Uni-Set

Dart Respiratory, Ocala FL

**REFERENCES**


