Standardization Issues: In Vitro Assessment of Nebulizer Performance

John H Dennis PhD MSc

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Summary

The delivery of nebulized drugs is poorly controlled and the choice of the most appropriate delivery device is poorly understood, particularly because of off-license prescriptions and a lack of evidence-based medicine. Standardized in vitro methods for measuring nebulizer performance have been adopted in Europe, by the 2001 publication of a European Standard, prEN13544–1. These standardized methods were subsequently incorporated within the European Respiratory Society nebulizer guidelines, which will provide clinicians with useful information to improve nebulizer therapies. Standards for measuring nebulizer performance should be considered in North America and elsewhere. Careful consideration should be given to either adopting the methods embodied in the European Standard or developing the basis for developing that standard further through the International Standards Organization. Either way, confusion among clinicians would be reduced and nebulizer safety and aerosol delivery efficiency increased by standardizing in vitro methods of nebulizer performance assessment. Key words: nebulizer, nebulization, aerosol, standard, standardization, testing, Europe, International Standards Organization, ISO, Comité Européen de Normalisation, CEN, in vitro assessment. [Respir Care 2002;47(12):1445–1455]

Introduction

Although delivering nebulized drugs to the lungs has been used for centuries in medical research, and nebulizers and nebulizer drugs have been commercially available throughout the past century,1 the delivery of nebulized drugs is still poorly controlled and poorly understood by the clinical community.

Prescription drugs delivered orally, intravenously, and via aerosol inhalation from metered-dose inhalers and dry powder inhalers undergo clinical trials to prove the drug’s safety and efficacy. This is not the case with the many drugs used for nebulization, which are prescribed off-license and bypass regulatory requirements. Nebulizers are regarded as cheap and convenient plastic devices that readily generate an aerosol (Fig. 1) that will contain whatever drug solutions or suspensions are placed in them for delivery to the respiratory tract. Rarely is the nebulizer delivery device specified on the prescription. Rather, only

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the drug solution volume and concentration are specified. This leaves open the choice of nebulizer by which to deliver the off-license drug aerosol. The decision of what device to use is often left up to the local doctor or nurse, and sometimes even a hospital clerk, to choose whatever device is either conveniently to hand or has become the hospital’s standard nebulizer for that period. The nebulizer is often chosen with little or no objective justification other than the manufacturer’s performance claims or, more often, simply the lower cost of a particular nebulizer. The reader should recognize that there is a wide range of performance among nebulizers. If, say, 2 mL of a given drug solution was placed into all available nebulizers, the dose delivered could vary greatly. The lack of regulation and understanding in matching the prescribed drug with the nebulizer implies that the quality, consistency, and control of the delivered dose are poor.

There are 2 main types of nebulizer, jet (or pneumatic) and ultrasonic, which have different operating characteristics (recently reviewed by Hess) and can be described in terms of their overall performance as either constant-output, breath-enhanced, or dosimetric. Each nebulizer brand has specific characteristics that determine its aerosol output, including total rate of aerosol output, rate of aerosol delivered to the patient, dead volume (solution remaining in the nebulizer after nebulization has ceased), and particle size characteristics. Some nebulizers are most efficient at delivering small droplets to the peripheral lung, some nebulizers are better suited to deliver larger particles in the upper airways, and, in my opinion, some nebulizers are not suited to drug aerosol delivery at all. But how is the clinician to know which nebulizer to use for which patient? What criteria can the clinician use to make an informed decision?

Many methods have been described to measure the “performance” of particular nebulizer designs. For instance, measurement of aerosol output using weight loss has been undertaken for decades and is still commonly used. However, weight loss measures both aerosol output and evaporated solvent, and evaporated solvent typically accounts for half of the weight loss over a nebulization period. In some particularly inefficient nebulizers, evaporation can account for more than 75% of the weight loss. Alternatively, total aerosol output can be estimated by measuring the amount of drug solution left in the nebulizer cup. This method can provide a measure of the total drug aerosol emitted and is not confounded by evaporative losses, but it does not reflect the aerosol delivered to the patient, as most nebulizers commonly allow inhalation of only 40–70% of the emitted dose. There is a similar problem with methods that collect all emitted aerosol on a filter, followed by subsequent analysis of the filtered residue. Though all these methods produce data, the results cannot reflect the in vivo situation. This, in my opinion, makes them weak methods on which to base a nebulizer standard, as the results are divorced from the clinical setting.

Measuring aerosol particle size is equally confusing. Cascade impactors, which are commonly used to measure aerosol particle size from metered-dose inhalers and dry powder inhalers, can drastically distort the aerosol size by causing full evaporation of the nebulized aerosol. Laser diffraction (scattered light) size measurement of aerosol droplets cannot take into account droplet evaporation, which is inherent in all constant-output aerosol designs. For both aerosol output and aerosol droplet size many different results are possible from the same nebulizer, depending on the measurement method used.

The relative merits of the various methods to assess in vitro nebulizer performance have been debated in the literature for decades, often by individuals or small groups with greater or lesser amounts of training in aerosol and clinical sciences. From all the different views one common message emerges, namely that the method used should reflect the amount and droplet size of aerosol received by the patient. In other words, the in vitro test should reflect the in vivo dose delivered. However, though that is a commonly held objective, over the past 50 years researchers have not naturally regressed to a commonly accepted nebulizer test method. And because nebulized drugs have escaped regulatory control, no national or international body had been commissioned to examine the science and produce standard methods. Or at least that was the situation...
until the early 1990s, when the United Kingdom’s standards body made the first attempt at standardizing test methods, by publishing a British Standard. Though the British Standard methods had limitations (Table 1) the existence of the published standard became a focal point for debate and progress. In the late 1990s the issue of standardizing in vitro methods to assess nebulizer performance was tackled more comprehensively by the European Standards Organization (Comité Européen de Normalisation or CEN), culminating in the research and development of new nebulizer in vitro test methods published as a European Standard.

The present review summarizes standardization issues inherent in the in vitro measurement of nebulizer performance, describes the scientific and clinical principles underlying the European Standard, introduces the principles underlying the clinical nebulizer guidelines recently published by the European Respiratory Society, and describes how the European Respiratory Society adopted the standard testing methods of the European Standard.

**Standardization Issues**

There may be a perception that “standardization” could be interpreted as making things the same: making them a standard size, shape, color, or, in the case of nebulizers, similar in terms of performance, as measured by aerosol output and aerosol droplet size. That is not the intended meaning of standardization in this review.

There are many types, designs, and brands of nebulizer, with a great range of aerosol output and droplet size. I regard this as a good thing, because different drug solutions and suspensions are targeted to different parts of the airways, in different doses. Therefore different nebulizer designs are needed for different patients and settings (pediatric versus adult, intensive care versus home care), with different delivered aerosol doses and different droplet sizes required for different patients and therapies. Thus a wide range of nebulizer designs and performances are needed, ideally with each nebulizer medication being matched to a particular window of nebulizer performance. However, difficulty arises when clinicians are faced with numerous devices and manufacturer claims of performance characteristics. How should a clinician make the choice of what nebulizer system is best suited to a particular patient or patient group for effective delivery of a particular medicine?

In choosing the ideal nebulizer to deliver a particular drug, the clinician should take into account the intended site of aerosol deposition (upper and/or lower respiratory tract), which largely determines the required aerosol droplet size, depending on the patient’s age and disease state, desired dose, treatment time, and patient compliance with the treatment. In addition, cost constraints can limit the choice of nebulizer. At present a major difficulty is that information on nebulizer performance is not presented to the clinician in any meaningful way.

Information on nebulizer output and aerosol droplet size can be entirely absent or only loosely described in marketing jargon (eg, “best performing nebulizer,” “clinically proven,” “preferred by over 90% of users”) without any scientific justification of the claims. Of course not all nebulizer manufacturers are so vague in describing the performance of their devices. Many manufacturers actively promote, or at least have available, technical literature on their devices. However, those performance data can be obtained with a wide variety of laboratory methods. However well-informed the clinician, performance data are very dependent on the method by which they were obtained—so

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**Table 1. Strengths and Weaknesses of British Standard 7711, Part 3, Specification for Gas-powered Nebulizers for the Delivery of Drugs**

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>First formal national standard relating to jet nebulizers</td>
<td>Focused attention on assessment of nebulizer performance and provided a platform for debate and technical research and development.</td>
</tr>
<tr>
<td>Adopted a chemical tracer rather than weight loss to evaluate nebulizer performance</td>
<td>Standard practice relied on weight loss, which grossly overestimated true aerosol output because of concurrent evaporation to compressed and ambient air.</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Weaknesses</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>No use of breathing pattern in assessing inhaled aerosol</td>
<td>This is particularly important for assessing the performance of breath-enhanced and dosimetric nebulizer designs.</td>
</tr>
<tr>
<td>Does not extend to ultrasonic nebulizers</td>
<td>Modern designs of ultrasonic nebulizers (eg, Omron nebulizer) have solved many past technical limitations and are expected to become more common as their advantages are recognized in the health care market.</td>
</tr>
<tr>
<td>Relies on laser diffraction to estimate particle size</td>
<td>Laser sizing does not account of solute concentrating effects, particularly in the smaller particles, and provides a volume/size distribution invarially larger than the solute size (dry particles) distribution, which is of far greater clinical relevance and interest.</td>
</tr>
<tr>
<td>Applies laser diffraction to size a “standing cloud”</td>
<td>Nebulizer aerosols rapidly evaporate in ambient air, such as the air entrained over constant-output nebulizers or through breath-enhanced nebulizers.</td>
</tr>
</tbody>
</table>
much so that the data may be meaningless, as with aerosol output measured by weight loss or solute loss, with or without breathing simulation. Yet that is usually the only type of information the clinician is expected to use in deciding about off-license nebulization of a drug. It is difficult if not impossible for the average clinician, who is not an expert in nebulizer design and function, to make an informed decision on which device is best for which patient. For that reason the focus in this review is to persuade the reader that some amount of standardization of in vitro aerosol measurement methods is desirable. Such standardization would provide a commonly derived data set for all nebulizer designs, which would (1) be more easily interpreted than the type of data currently available, (2) help clinicians determine the most appropriate nebulizers for particular patients and patient groups, and (3) improve patient safety and aerosol delivery efficiency.

At the risk of laboring the point for the need for standardizing nebulizer performance testing, consider the following analogy with the automobile industry. Cars come in a range of shapes and sizes and are intended for different purposes. Most car buyers know what basic design they require, but choosing the exact brand and model can be difficult. Like nebulizers, the manufacturer's marketing information is invariably biased toward its own product. Though this may make interesting reading for the enthusiast, it should not be relied upon for an objective decision. We can rely on reviews by experts who offer their opinions on subtle differences between models, but those views are individual and invariably biased by previous prejudices and current affiliations. Consider the information available for estimating fuel economy. If this important performance criterion were left solely up to the manufacturers to provide, they would no doubt as an industrial group regress to making the measurement starting from the top of a mountain with a tailwind in order to bias the fuel economy figure as far as possible. That does not happen because standardized test methods for fuel economy have been developed to gain more realistic and comparable data. We must rely on objective information supplied by standardized methods to make an objective and fully informed decision. For example, data on trunk (called “boot” in the United Kingdom) space, acceleration, servicing costs, and depreciation are independently obtained. The methods for obtaining these data are refined to be as realistic and repeatable as practicable. Data that prove unrealistic are of little use. Methods that cannot be repeated are of little value. What is true for the automotive industry and marketplace is largely true for the nebulizer industry and marketplace.

To date there has been little, if any, standardization in the nebulizer industry and marketplace. I believe the industry would welcome standardization, as would most clinicians and nebulizer users. Standardization of in vitro performance measures would improve patient safety and aerosol delivery efficiency, and, in the long term, standardization can help provide a more solid foundation for development of better nebulizer technologies, because manufacturers will know that the marketplace is better prepared to recognize and appreciate the real benefits of new technologies. At present if a manufacturer produced a better nebulizer, how would the clinician know? It would just be absorbed into the marketplace as yet another “best performance” nebulizer claim, with perhaps a few supporting papers written by individuals with personal bias and affiliation. It is for these reasons that some standardization is required.

**European Nebulizer Standard**

The European Standard developed over a period of 6 years, involving all European national standards bodies (eg, United Kingdom’s British Standards Institution, Netherlands Organization for Applied Scientific Research) working within CEN, the European umbrella organization. Most scientists and clinicians with a serious interest in nebulizer testing and clinical application were involved, either directly or indirectly. For the first time, a critical mass of clinical and scientific experts were brought together to focus on how best to standardize the measurement of nebulizer performance. Though the European Standard on nebulizers addresses a number of regulatory issues, most are beyond the scope of the present review. What is important here is that the European Standard facilitated the development of in vitro testing methodologies that were thoroughly discussed and evaluated prior to acceptance by the European clinical and scientific aerosol community. Aspects of the European Standard have been described elsewhere. Some of the more important principles are introduced and summarized below.

**Nebulizer Versus Nebulizer System**

The European Standard recognizes that different nebulizers will deliver different doses of drug to the same patient, even if all conditions such as breathing pattern and nebulizer fill volume are controlled. This is because some nebulizers are inherently more efficient than others. For example, consider the most common nebulizer design, the constant-output nebulizer, which probably accounts for more than 70% of the nebulizers in home and hospital use today. A constant-output nebulizer emits aerosol at a constant rate until the volume of drug solution in the nebulizer cup is so small that nebulization ceases. The rate of aerosol output is constant, regardless of whether the patient is inhaling, breath-holding, or exhaling. This implies that for at least half the duration of operation the nebulizer is emitting aerosol into the ambient air. Not only is this extremely
wasteful, it is an important source of air pollution. Breath-enhanced nebulizers, on the other hand, release more aerosol during patient inhalation than during breath-hold or exhalation and thus are inherently more efficient. Dosi- metric nebulizers are the most efficient because (at least in theory) aerosol is released only during inhalation, so the entire emitted dose is delivered to the patient.

However, it is not only the nebulizer design that is important in determining the performance of the nebulizer; the characteristics of the nebulizer itself can be critically important. With a jet nebulizer the greater the flow of compressed air through the nebulizer, in general, the greater the aerosol output and, usually, the smaller the particle size. So the compressor is an integral part of the nebulizer system. Another important aspect of the nebulizer system is the design and use of the mouthpiece (eg. whether the mouthpiece is valved for exhalation), which can significantly influence the quantity and quality of aerosol delivered to the patient. Alternatively, the mouthpiece might be replaced by a face mask, which can greatly reduce the amount of drug effectively delivered to the patient.

The European Standard recognizes the importance of the nebulizer system rather than simply the nebulizer itself. For this reason the European Standard specifies that nebulizer manufacturers should test performance of the nebulizer system as they intend it to be used. So, for example, if a nebulizer manufacturer sells a nebulizer sometimes with a mouthpiece and sometimes with a face mask, both of those 2 nebulizer systems need to be tested for aerosol output and size. Similarly if the nebulizer is recommended for use with various compressed air flows, the manufacturer is required to test each nebulizer system with the range of recommended air flows—the minimum, maximum, and typical average flow. This requirement to test each permutation can impose a substantial range of testing variables, but each permutation relates to a specific clinical condition of use to which the manufacturer is targeting the nebulizer product. Adoption of a nebulizer system concept will dissuade manufacturers or researchers from publishing performance information without also making reference to the system in which it was tested.

The European Standard does not require testing all nebulizer designs for their ability to nebulize all drugs. Most commonly prescribed nebulizer drugs are in aqueous solutions that also contain excipients and usually some concentration of sodium chloride. Some formulations are suspensions, with small, nearly colloidal solid particles within an aqueous solution, usually with excipients and sodium chloride. Most formulations intended for nebulization (by design or prescribed off-license) behave much like a simple salt solution, though admittedly a few drug solutions and suspensions do not because they are either extremely viscous, froth, or foam during nebulization, or have some other physical characteristic that causes atypical behavior.

However, those are the exception. The European Standard recognizes that testing all forms of drug solutions and suspensions with all of the nebulizer systems combinations would be unreasonably burdensome. The practice adopted within the European Standard was to use a single test solution for all nebulizer system permutations. The solution adopted was a low concentration of sodium fluoride, which was chosen because: it has similar properties to sodium chloride, which is commonly used in nebulizer drug formulations; it is relatively rare in most laboratory environments, so contamination from other sources is minimized; and electrochemical analysis of sodium fluoride concentration (using a method similar to pH measurement) is relatively simple, low-cost, and sufficiently analytically sensitive.

Measuring Aerosol Output and Aerosol Droplet Size Using the Methods in the European Standard

In vitro assessment of nebulizer output has been poorly understood and characterized, and numerous methods have been described to estimate output. Recently, a European Standard was published and is believed to contain methods for reproducible and robust in vitro measurement of nebulizer aerosol output and droplet size.

Aerosol Output

Figure 2 illustrates the European Standard methodology for measuring aerosol output. The nebulizer system is attached to a breathing simulation device. A low-resistance electrostatic filter (simulating the patient) is placed between the breathing simulation device and the nebulizer system. The intention is that aerosol collected on that filter represents aerosol delivered to the patient under clinical conditions. The standard breathing cycle is a simple sinus flow pattern of 15 cycles per minute and 500 mL per cycle. This pattern was adopted because it is relatively simple to simulate and reproduce. Other breathing patterns were considered (eg. square waves, various inspiratory/expiratory ratios), but none was thought more appropriate as a single measure than the simple sinus flow pattern. Though this pattern is specifically defined in the European Standard, the methods used can be adapted to virtually any other breathing pattern. Whatever the breathing pattern, the nebulizer is filled with a volume of test liquid that contains a trace amount (1%) of sodium fluoride. With the breathing simulation device running and an electrostatic filter in place, any aerosol generated by the nebulizer system that is drawn into the breathing system (the analogy of being inhaled by a patient) is collected on the filter. The fluoride residue on the filter can then be quantified.
Fig. 2. Schematic of Comité Européen de Normalisation (CEN) methodology to measure nebulizer aerosol output. Aerosol output is subjected to sinus flow breathing simulation, and the aerosol is collected onto low-resistance electrostatic filters. The aerosol contains trace concentrations of sodium fluoride, which is quantified electrochemically. rpm = respirations per minute. (Adapted from Reference 12.)

**Aerosol Particle Size**

Figure 3 illustrates the European Standard methodology for measuring aerosol particle size. A low-flow cascade impactor is placed in line with the nebulizer system. The nebulized fluid contains a trace (2.5%) of sodium fluoride. Instead of using the dynamic air flow pattern of a breathing machine, a constant simulated inhalation flow of 15 L/min is applied, which is thought to represent a typical mid-inhalation flow rate. The cascade impactor samples a 2 L/min (2/15) fraction of the total flow. The aerosol droplets deposit according to size in the stages of the cascade impactor, and the amount of fluoride residue on each stage is quantified. Table 2 presents a sample set of cascade
## Table 2. Worked Example of Data Obtained from a Graseby/Thermo Andersen Low-Flow Cascade Impactor

<table>
<thead>
<tr>
<th>Stage</th>
<th>Amount of Drug or Salt Assayed by HPLC on Each Stage (μg)</th>
<th>Calculations to Process Size Distribution Data</th>
<th>Cut-Point of Each Stage (from the impactor manual) [Dp (μm)]</th>
<th>Cumulative Summation of Material (derived from Column C) [% &lt; Dp]</th>
<th>Proportion of the Aerosol on Each Stage derived from Column B by Bstage/Btotal × 100% [V/V%cut (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top</td>
<td>0.09</td>
<td></td>
<td>8.80</td>
<td>50</td>
<td>1.96</td>
</tr>
<tr>
<td>Stage 1</td>
<td>0.09</td>
<td></td>
<td>0.85</td>
<td>1.32</td>
<td>98.0</td>
</tr>
<tr>
<td>Stage 2</td>
<td>0.11</td>
<td></td>
<td>0.36</td>
<td>21.3</td>
<td>96.1</td>
</tr>
<tr>
<td>Stage 3</td>
<td>0.41</td>
<td></td>
<td>0.41</td>
<td>14.8</td>
<td>93.7</td>
</tr>
<tr>
<td>Stage 4</td>
<td>0.41</td>
<td></td>
<td>1.00</td>
<td>11.44</td>
<td>85.4</td>
</tr>
<tr>
<td>Stage 5</td>
<td>0.87</td>
<td></td>
<td>1.77</td>
<td>21.34</td>
<td>6.61</td>
</tr>
<tr>
<td>Stage 6</td>
<td>0.87</td>
<td></td>
<td>7.67</td>
<td>33.25</td>
<td>18.31</td>
</tr>
<tr>
<td>Stage 7</td>
<td>0.72</td>
<td></td>
<td>0.38</td>
<td>120</td>
<td>35.5</td>
</tr>
<tr>
<td>Stage 8</td>
<td>0.06</td>
<td></td>
<td>0.11</td>
<td>0.93</td>
<td>7.73</td>
</tr>
<tr>
<td>Final</td>
<td>0.05</td>
<td></td>
<td>0.06</td>
<td>1.24</td>
<td>0.96</td>
</tr>
</tbody>
</table>

HPLC = high performance liquid chromatography
Dp = particle diameter

*Follows plotting of cumulative distribution curve against size

Mass median aerodynamic diameter (MMAD) = 4 μm

(Adapted from the Graseby/Thermo Andersen Maple 280 cascade impactor operator manual)

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### European Respiratory Society Guidelines

#### on the Use of Nebulizers

The European Respiratory Society Guidelines are intended to provide a more clinically representative measure of nebulizer output, based on the European Respiratory Society (ERS) guidelines. In vitro methods in the European Standard are used to assess the advantages of standardizing in vitro methods for different nebulizers. The ERS recommends that clinical studies of nebulizers be performed using the clinical principles of nebulizer output, and describes these principles underlying the clinical evaluation of the nebulizer. The ERS also provides guidance on how to use the guidelines for clinical decision-making.

### Clinical Relevance of the European Standard in Vivo Methods

It is not known how well the currently defined CEN test conditions will predict clinical performance. This can only be established through an appropriate clinical study. However, the agreement of a number of leading clinicians supports the use of the ERS guidelines in clinical decision-making. The ERS guidelines provide guidance on how to use the guidelines for clinical decision-making, and to be clinically relevant as practicable. Preliminary work in vitro shows that results obtained using the ERS guidelines can be compared with those obtained using other methods, but further research is required to establish the accuracy of these comparisons.

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improving conditions for the elderly, which are derived cumulative and normalized size distributions such as those depicted in Figure 4.
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Fig. 4. Cumulative and normative distribution curves obtained from sample aerosol particle size data in Table 2. The mass median aerodynamic diameter is the particle size (in μm) obtained at the 50% cumulative undersize. Dp = particle diameter, conc = concentration. (Courtesy of Cora A Pieron PhD.)

dience was pulmonary physicians, the message was also aimed at all health care workers who are involved in delivering nebulizer treatments. The guidelines provided recommendations based on scientific and clinical evidence, and identified areas of ignorance where present practice is based on tradition or opinion rather than on scientific evidence. It was also hoped that by identifying gaps in present knowledge the guidelines would spur clinical scientists to undertake new trials to guide future practice. Full details of the background of the guidelines can be found in published supplements from the technical14 and clinical15 workshops and in the ERS Guidelines.12

For the present discussion the most important part of the ERS Guidelines is their technical reliance on the methods in the European Standard, which offer, for the first time, the opportunity to obtain a set of aerosol output data for each nebulizer sold in the European market—a comprehensive data set commonly derived from standardized in vitro methods. Hopefully each set of nebulizer performance data will closely reflect the in vivo performance. Further, the ERS clinical guidelines have adopted the distinction in the European Standard regarding the difference between a nebulizer and a nebulizer system, and the ERS clinical guidelines rely on data obtained from complete nebulizer systems.

The availability of clinically representative in vitro methods has led to the establishment and implementation of standard operating practices as a means of improving the efficacy of nebulizer therapy. These standard operating practices are embodied in the ERS clinical guidelines and are described below.

Type Testing Using the European Standard

Nebulizer manufacturers in Europe are now required to test each of their nebulizer systems with a reference solution according to the European Standard. This will result in standardized information being supplied with every nebulizer. This information will include:

1. Description of the nebulizer system, including the flow rates and fill volumes tested
2. Rate of aerosol output and total aerosol output
3. Droplet size distribution curve, from which can be obtained the median droplet size, droplet geometric standard deviation, and percentage of aerosol mass within any given range (ie, > 5 μm, 2-5 μm, < 2 μm)

As mentioned above, the in vitro methods on which the European Standard is based are designed to reflect clinical conditions as closely as possible. The consistency of methods to obtain this in vitro information through the European Standard will essentially provide a type test of each nebulizer system, which will allow meaningful comparison of the performance of the various nebulizer systems and thus guide the optimal choice and use of those systems in clinical practice.

There are some important limitations in interpreting test data supplied by manufacturers complying with the European Standard. The first is that the data relate only to drug solutions that have properties similar to saline. Test data cannot be readily extrapolated to suspensions (eg, budesonide) or to solutions that have substantially greater viscosity than saline (eg, some antibiotics). The second is that the rates and amounts of aerosol delivery are obtained with
a simulated adult healthy breathing pattern, and those data cannot be readily applied to pediatric applications or diseased adults. The test methods adopted within the European Standard are sufficiently flexible to accommodate additional test configurations.

Characteristics of “Good” and “Bad” Nebulizer Systems

Nebulizer systems offer a wide range of performance, and how “good” or “bad” a system depends on what it is intended to do. For example, if a system were required to deliver the maximum amount of useful aerosol (droplets between 0.5 and 5 μm) in the minimum amount of time, with a minimum of inconvenience, then the characteristics of a “good” system would include:

1. Fast nebulization rate, implying that the maximum amount of nebulized aerosol is potentially available to the patient over any given time
2. Minimum waste of drug aerosol, implying that maximum amount of aerosol is delivered to the patient and as little as possible is emitted to the environment
3. Low dead volume, implying that a high percentage of the fill volume will be delivered to the patient
4. Well-defined droplet size distribution

If, however, the same system were required to deliver only a modest volume of drug aerosol, then the system above becomes “bad” because such an efficient system will deliver an unnecessarily large aerosol dose, with possible increased local and systemic adverse effects.

The ERS Guidelines recognize that consideration must be given to matching nebulizer drug delivery to the performance of nebulizer systems. This requirement varies according to the needs of different patient groups and stages of disease. The 2 main factors to take into account are:

1. How much nebulized drug is ideally required for delivery to the patient?
2. The droplet size required to maximize delivery to the intended site of action. Droplets <5 μm tend to deposit peripherally, whereas droplets around 5 μm will mainly deposit in central airways.

The ERS Guidelines recognize that little clinical evidence exists to answer these questions, and it is therefore difficult to choose the ideal nebulizer system for a given application. So the Guidelines recommend that a scheme be developed to define the best available nebulizer systems for various therapies, to reduce variability in nebulized dose delivery, and thereby improve clinical practice.

How to Select the Optimal System for a Given Patient Group or Specific Use

All health care systems throughout Europe currently have some system by which nebulizer drugs are prescribed for each clinical application. In addition, all prescribers and users of nebulizer drugs will commonly have experi-
ence using one or more nebulizer systems for each clinical application. Local practices will differ greatly, possibly even within an institution. Therefore the ERS Nebulizer Guidelines recommend that a standard operating practice be adopted for each nebulizer system in use. This would provide a baseline in determining the clinical effectiveness of each nebulizer system for each given application. That information could then be used to assess potential improvements to the nebulizer system.

Implementation and Use of Standard Operating Practice As a Means to Improve the Efficacy of Nebulizer Therapy

Standardize the Way Current Nebulizer Systems Are Used

If health practitioners can agree on a standard operating practice for the way in which nebulizer systems are used locally, then they can be sure that future clinical outcomes are patient-specific, rather than due to a change in drug output from the nebulizer. Nebulizer manufacturers can provide advice on the optimal operation of particular nebulizer systems.

Assess Drug Output from the Current Nebulizer System

The scarcity of useful in vitro data describing nebulizer system performance has perhaps contributed to arbitrary choices of nebulizer systems. However, the standardization of nebulizer aerosol output and droplet size measurements made possible by the European Standard allows any given standard operating practice to be reassessed. For a specific clinical application the standard operating practice can be used in conjunction with data from the manufacturer to derive the dose delivered by that standard operating practice. That dose can be the total output, or it can be modified by the fraction of the aerosol in the optimal size range to determine a “useful” dose. If appropriate, one should also consider the potential systemic exposure from droplets not in the “useful” range, either by being too large and therefore depositing in the oropharynx, or by depositing in an inappropriate region of the lung and thus being directly absorbed into the systemic circulation and providing minimal local efficacy. Based on this approach, standard operating practices can be reassessed to see whether drug delivery can be further optimized by a change in one of the operating variables (e.g., gas flow).

Evaluate Alternative Nebulizer Systems

This information can be re-evaluated over time, as more efficient or cheaper nebulizers emerge. Consideration can then be given to altering prescription convention and/or adopting alternative nebulizer systems whose nominal delivered dose and droplet size (the standardized in vitro data from the manufacturer) are suited to a given clinical application. However, as with standardizing the way current nebulizer systems are used, substantial changes to standard operating practice should be monitored by appropriate follow-up of outcomes such as clinical benefits and adverse effects.

Future Developments in Nebulized Drug Delivery

The task force drafting the ERS Guidelines anticipated that technical advances would drive improvements in nebulizer design. These performance advancements are being embodied in the next generation of nebulizers, which are beginning to enter the market and will compete with more traditional jet and ultrasonic nebulizers. At the very least, these new devices will offer substantial improvements in aerosol delivery efficiency. Though these systems can improve the quality of nebulizer therapy, there are risks if they are adopted with insufficient consideration of the consequences of efficiency improvements. However, if local practices adopt the above recommendations of instituting and reviewing standard operating practices, new and improved nebulizer therapies could be safely integrated with net benefits to patients. It is likely that newer, more efficient systems will deliver inhaled drugs more effectively and thus reduce the waste and the cost associated with inefficient systems. Clearly, standardization in measuring in vitro performance is required to safely make use of these new nebulizer technologies.

Summary

Standardization of in vitro methods for measuring nebulizer performance would greatly reduce confusion and improve safety and efficacy of nebulizer therapy. The recently published European standard specifies in vitro methods for measuring and reporting nebulizer performance, and the data are expected to closely correlate with in vivo measurements of delivered dose and droplet size. The independent development of the ERS Guidelines took advantage of the European Standard and relied on the in vitro measurement methods therein to develop and recommend a common-sense strategy to improve clinical practice of nebulizer therapy throughout Europe.

Both the European Standard and ERS Guidelines are, by definition, intended to influence and improve the standard of nebulizer therapy in Europe. In practice, the in vitro methods described are universal, as are the recommendations to improve clinical practice. My final words to readers of Respiratory Care in North America and elsewhere outside Europe are that the standardization issues that have
been tackled in Europe are universal and apply equally in North America. If there is no good reason to adopt alternative in vitro methods for assessing nebulizer performance, then the methods in the European Standard can be adopted in North America or perhaps even by the International Standards Organization. This evolution would allow for any required changes and improvements to the European in vitro assessment methods that might become evident.

Some standardization in assessing in vitro nebulizer performance in North America is inevitable and required. However, the nebulizer manufacturing industry is very small in comparison to the pharmaceutical industry and can ill-afford a plethora of testing regimens. In my opinion there should be only one recognized standard for in vitro assessment of nebulizer aerosol. Developing a separate standard set of in vitro methods for North America defeats the purpose and would only serve to confuse the issues. I expect that the North American standards bodies will look closely at the methods adopted in Europe, and they should consider 2 options:

1. The in vitro methods accepted in Europe could simply be adopted in their entirety in North America, or
2. If fundamental problems are discovered with the European methods, or alternative methods are found to be more closely correlated with in vivo response, then a dialogue and cooperation among interested organizations in North America, Europe, and elsewhere could build a new set of methods in an international standard.

Either way, a single set of in vitro methods would result, which could be used in the absence of clinical trials to guide clinicians in choosing appropriate nebulizer systems.

The worst-case scenario would be that different in vitro testing methods (that yield different results for different nebulizer systems) be adopted in different countries. This would act to retard progress and increase confusion, and therefore must be avoided.

At present it is difficult if not impossible to meaningfully compare in vitro nebulizer performance data because of confusion about methodology and nebulizer operation. If a single in vitro measurement method such as the CEN standard were widely adopted, then nebulizer output data from different nebulizer systems could be meaningfully compared and evaluated.

**Discussion**

O’Riordan: I certainly agree with you that these European standards are much more sophisticated than anything that’s gone before, but nevertheless I want to sound a note of caution, which is that when we look at lung modeling data for aerosol deposition, we’re relying on the work of investigators who use monodisperse solid particles in healthy individuals. With nebulizers we’re usually dealing with unstable, polydisperse, aqueous aerosols in people with diseased lungs. We therefore don’t really have a great way of linking in vitro to in vivo data, so I think we should use the standards to work backward.

For example, let’s say you do a study of cystic fibrosis and you prove that a particular dose of tobramycin is safe and effective. Then if that nebulizer becomes unavailable, you can use it...
those data to find an nebulizer that is as close as possible to the nebulizer that was used in clinical trials, assuming that you’ll get comparable safety and efficacy. It’s much more risky to use the standards as absolutes, in such a manner that someone may claim, “Well, I’ve just designed a nebulizer, and it’s got this particle size and this output, and therefore it’s better than the one that was used in the original clinical trial.” That’s a big assumption. I think we should play it safe and try to duplicate the nebulizer that had been used in clinical trials, because at least we know the safety and we know the efficacy. If somebody comes up with a nebulizer that’s supposedly twice as good, they should have to do a clinical trial to support that claim.

Dennis: I think you’re talking about a very specific application, and I think that would be a matter for a specific review body to look at. I’ve got no issue with it. What I’m getting at is the idea of leveling the playing field and getting one consistent and meaningful set of methods to describe a nebulizer’s performance.

Fiel: I think the concept of standards is absolutely necessary for where we’re going, in trying to pull together the clinical outcome and the production of the various devices that are coming along. Still, I think that’s a really good point that Tom O’Riordan made. And how it’ll work out in the clinical arena remains to be seen. Up until now most of what clinicians have dealt with has been bronchodilators, where it really doesn’t matter where and how you deliver, but it’s going to be a whole different field soon and we’re in for some problems if we do not standardize. John, do the European Standards have specific methods for the breath-actuated nebulizers?

Dennis: The breath-actuated nebulizers will just slip into the testing regimen for flow cycles, because they come on during inhalation and shut off during exhalation. So they will work within the testing method. For example, the Halolite and the Aerol-Eclipse both trigger during inhalation, though there may be an issue with whether they trigger soon enough at the lowest inspiratory flows.

Dennis: I was really interested in your engineering solution to make smarter physicians. To borrow a phrase from Alessandro [Gomez], I think we are heading for a “Coulombic explosion” with new nebulizer technology. I think a comparable issue is administration of antibiotics. There are specific indications for the use of an antibiotic, and then there are also specific indications for when you don’t use them. I think for physicians it might be very helpful if nebulizer solutions came out with specific indications for which population they should be used with, how they should be used, and in which situations they should not be used.

Dennis: The ERS Guidelines look at the evidence for that and they make summary statements and recommendations.

Smaldone: I’m getting nervous, I have no problem with standards, but to me as an engineer, one standard is to look at a nomogram and the conditions for the measurement are there, and the data are there, and you do what you want with it. My problem with the so-called “standards” that have been discussed here are adjectives such as “meaningful,” “appropriate,” “better,” “worse,” and “recommended.”

Dennis: “Consistent.”

Smaldone: “Consistent” to me is simply the quality of the laboratory. If there’s a nomogram with outputs on it, they’ll have plus-minus sign on it, and there’ll be a statement of—

Dennis: Oh, I meant consistent between laboratories—when different laboratories test the same nebulizer system and the results are similar, the results are consistent.
what I'm talking about, that's what the ERS Guidelines are targeted at, and that's what we'll use the European Standard methods to provide: consistent information on aerosol output and droplet size from each nebulizer system. Consistent information that allows us to at least compare like with like. That information is not available at the moment.

Gomez: I want to comment on standardization of droplet size measurement techniques. The ERS standards are certainly acceptable and should be enforced. You mentioned that the laser diffraction technique may not be the best. If you are referring to the Malvern instrument, in the "droplet community" the Malvern has been almost completely supplanted by phase Doppler anemometry, which simultaneously measures droplet size, droplet velocity, and gas velocity, so that we have all the variables that are relevant for inertial based deposition.

Dennis: That works for you, but we're dealing with an aerosol that's evaporating at the same time that we're interested in the solute concentration, which you can't measure with phased Doppler, because the solute is concentrated. You don't know how much a droplet has been concentrated by, so a 2-μm particle might contain as much drug as a 5-μm particle. There's a dynamic operating that you can only measure by cascade impactor, at least with the existing technology.

Gomez: Wait a minute. You can model based on evaporation loss, because the volatile solvent evaporates and the solute stays behind.

Dennis: There's a couple of guys who have put their whole careers into such modeling, and they are still struggling away to try to get their modeling results to match the experimental data. It's not my field, and I admit it's possible, but it's certainly complex and is still indirect.

Fink:* It occurs to me that product information for many commercial aerosol products use similar units of measure for very different methodologies, on occasion using totally inappropriate devices to measure particle size. For instance, systems designed to make gravimetric measures of dry powder are totally inappropriate for jet nebulizers aerosolizing normal saline. This is how you see claims of 0.9-μm particles from a nebulizer that produces particles that measure > 5 μm by direct assay with a standard cascade impactor. Unfortunately, the manufacturer's data are often the only data the consumer has to make the device selection decision. In our laboratory we have tested a variety of nebulizers used for home care, finding inhaled mass ranging from 6 to 55%, with no relevant data in the manufacturer's literature. Do clinicians need to know that their choice of nebulizer may result in a 10-fold difference in drug delivery for their patient? Some standard for comparative measurement and reporting may have merit.

Witek:* My comment covers all of the presentations this morning, but particularly Gerry's [Smaldone] thoughts about marketing, advertising, and adjectives. I think it's important to understand that words such as "superior," "equivalent," and "noninferior" have very specific meanings in the design of a study, with respect to a priori statements on how your statistical analysis is designed. The important thing is that we in the industry have to define those and state such aspects a priori, and when we meet those requirements, then we're allowed to use those adjectives. Consider some of the data we saw today, for example: what's an "equivalent" response in FEV₁ [forced expiratory volume in the first second]? In a simplified example, some may say you take your peak response relative to placebo, and if it falls within a third of that response, you may have "equivalent" response in FEV₁. So, in some sense, with regard to the clinical data, there is some degree of a level playing field in that you need substantial evidence on what you say a priori you are testing.

Dolovich: I want to follow up on Jim Fink's comment. The Canadian standard that we developed for spacers has built into it testing the spacer with 3 drugs, so that we can compare different devices with the same type of drug. The manufacturer has a choice within the drug category, but it is anticipated that some drugs tested will be common to many of the manufacturers. Is that type of requirement also part of the CEN standard?

Dennis: Testing with drugs is not part of the CEN standard. The CEN standard is for generic testing of nebulizer performance, using a simple salt solution. However, the CEN standard allows for testing of drugs, since the analysis part can be adapted to high-performance liquid chromatography or other methods.

McMahon:* From a manufacturer's perspective, I believe you will find support for implementing standardized test methods for nebulizers. I do not believe the data will answer all of a clinician's questions; they will not dictate which nebulizer to use in various clinical applications. They should, however, help with credibility in advertising and literature, specifically in regard to measurements of MMAD [mass median aerodynamic diameter] and the percentage of respirable droplets. Several variables, including temperature, humidity, and flow rates, influence MMAD and the percentage of

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respirable droplets, so data from testing in various laboratories may not match what is in the advertising and literature for the device. So it would seem beneficial to have a standard test for nebulizers to determine MMAD and percentage of respirable droplets. It would clarify the test conditions used to obtain the data in advertising and literature.

**Dennis:** Yes, I agree. A nebulizer that came into Britain from Italy supposedly had 100% respirable aerosol. It was fantastic, and it was all the rage. But they had measured the particle size using saline and the TSI particle sizer, so it was just dry powder generated by the method of measurement! Not clinically representative at all. And they got away with it! They sold and they made money. People talked about the adjectives. I've deliberately tried not to use adjectives, and generally tried to say that “good” and “bad” can mean the same thing, depending on the application. It's the application the clinician should focus on.

**Berg:** But there's nothing in the standards that indicate that you should test any drugs.

**Dennis:** I agree in part. The main purpose of the CEN standard is to end up with a CE mark [Conformite Européene mark, on a product, that indicates the manufacturer has conformed with European product safety regulations] and say it passes the criteria of safety, plastic robustness (for instance, parts aren't going to fall off into a patient’s lung), electrical safety, and all the other things that any safety organization would normally look at. But the CEN standard also needed some measure of aerosol output and size. Besides those other things, the CEN standard was always focused on providing a measure of output, some measure of nebulizer “performance.” We tried to make sure the methods were as useful as we could make them.

The manufacturers will have to test for the CEN standard in any case, whatever the method. You can throw drugs into the equation and collect drug information, if you want to extend the CEN testing to that as well as the generic simple salt solution. So, in summary, though the primary purpose of the whole CEN standards organization and funding is for type testing (which is really behind-the-scenes manufacturing stuff), it has been adapted so its results become clinically useful, which they otherwise would not have been.

**Berg:** But there's nothing in the standards that say that you should test any drugs.

**Dennis:** It's actually in the standard that you can, but that drug information would not be reflected in the output generated for the CE marking, which is restricted to the output obtained with the simple salt solution. But you could extend the CEN study tests to using drugs in the nebulizer cup. The drug could change the output if, for example, it were more viscous. Alternatively, the drug could be a suspension. It is written in the CEN standard that you can apply it generally, but the CEN standard also warns against extrapolating the salt solution results to what will happen with the nebulizer drugs. If you want to know how a certain drug will perform in a certain nebulizer, test the drug or ask the manufacturer for the data. That's what the standard and guidelines recommend.

However, what the CEN standard does require as a minimum is that the manufacturer provide detailed output data (for simple salt solution, not drugs) on the nebulizer packaging, in order to get a CE mark. This provides the level playing field. This provides simple aerosol output and droplet size information for every nebulizer system with a CE mark, which is clinically useful comparative information. I believe this is an advancement on the current situation, which is very confused.

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