Canadian Standards Association standard CAN/CSA/Z264.1-02:2002: A new voluntary standard for spacers and holding chambers used with pressurized metered-dose inhalers

Myrna B Dolovich P Eng[1], Jolyon P Mitchell PhD FRSC (UK) CChem[2]

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A new Canadian standard (CAN/CSA/Z264.1-02:2002) has been published with the purpose of helping to ensure the safety, efficacy and functionality of spacers and/or holding chambers. They are prescribed for use by spontaneously breathing patients for the treatment of various respiratory diseases where medication is delivered to the lungs using pressurized-metered dose inhalers. This consensus standard was developed with the support of pharmaceutical companies and manufacturers of spacers and holding chambers, and with the help of clinicians, retail pharmacists and representatives of patient advocate bodies associated with respiratory diseases and the dissemination of information related to the treatment and the delivery of inhaled medications. Advice was also sought from expert groups outside of Canada to ensure that the standard would be relevant internationally. Whereas monographs in the pharmaceutical compendia and guidance documents published by regulatory bodies provide information that is largely about the drug product and inhaler, this is the only standard whose focus is primarily on these add-on devices. The purpose of the present review is to highlight the main features of the standard for clinicians by describing its scope, the tests that are intended to assure the robustness of the construction of these devices, the type of testing that is specified to establish in vitro efficacy, and the recommendations for the marking and labelling of the device and its associated packaging. Manufacturers who test their products to this Canadian Standards Association standard will be able to provide performance information about add-on devices to the clinician, facilitating an informed decision when selecting devices for patients.

Key Words: *Aerosols: Holding chamber; Inhaler; In vitro testing; Metered dose inhalers; Respiratory drug delivery; Spacer; Voluntary standard*

La norme CAN/CSA/Z264.1-02:2002 de la *Canadian Standards Association* : Une nouvelle norme volontaire pour les espaceurs et les aérochambres utilisés avec des aérosols doseurs pressurisés

Une nouvelle norme canadienne (CAN/CSA/Z264.1-02:2002) a été publiée afin de contribuer à garantir l'innocuité, l'efficacité et la fonctionnalité des espaceurs ou des aérochambres. Ceux-ci sont prescrits afin d'être utilisés par des patients qui respirent spontanément, dans le traitement de diverses maladies respiratoires pour lesquelles le médicament est délivré aux poumons au moyen d'aérosols doseurs pressurisés. Cette norme consensuelle a été élaborée avec l'appui de sociétés pharmaceutiques et de fabricants d'espaceurs et d'aérochambres et avec l'aide de cliniciens, de pharmaciens de détail et de représentants d'organismes de défense des patients associés aux maladies respiratoires et à la diffusion d'information reliée au traitement et à la délivrance de médicaments par aérosol. Des conseils ont également été demandés à des groupes d'experts de l'extérieur du Canada, afin de garantir que la norme soit pertinente sur la scène internationale. Tandis que les monographies des compendiums de produits pharmaceutiques et que les documents d'orientation publiés par des organismes de réglementation fournissent de l'information portant surtout sur le produit pharmaceutique et l'aérosol, c'est la seule norme à être axée sur ces appareils complémentaires. La présente analyse vise à souligner les principales caractéristiques de la norme aux cliniciens par une description de sa portée, des tests prévus pour garantir la robustesse de construction de ces appareils, le type de tests conçus pour en déterminer l'efficacité *in vitro* et les recommandations relatives au marquage et à l'étiquetage de l'appareil ainsi qu'à son conditionnement. Les fabricants qui mettent leurs produits à l'essai conformément à cette norme de la *Canadian Standards Association* pourront donner de l'information sur le rendement de leurs appareils complémentaires au clinicien, ce qui facilitera une décision éclairée au moment de faire un choix pour le patient.

Spacers and (valved) holding chambers (S-HC) are widely prescribed add-on devices for use with pressurized metered-dose inhaler (pMDI) medications used in the treatment of respiratory conditions such as asthma and chronic obstructive pulmonary disease (1,2). A variety of devices has appeared for sale in Canada during the 20-year period since the start of the widespread use of S-HCs, reflecting the desire of manufacturers to improve product performance and to extend their use to all patient age groups. Selected S-HCs currently available in the Canadian marketplace are listed in Table 1. Although many published laboratory studies with S-HCs exist (3), there is a lack of information on their performance when obtained under rigorously standardized conditions, making comparisons difficult. Factors influencing medication delivery include patient category (eg, infant, child or adult), ability to coordinate inhalation with actuation of the inhaler and the breathing maneuver

[1]*Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton;* [2]*Trudell Medical International, London, Ontario*
Correspondence and reprints: Professor Myrna B Dolovich, McMaster University, Faculty of Health Sciences, 1200 Main Street West, HSC 1V18, Hamilton, Ontario L8N 3Z5. Telephone 905-521-2100 ext 73454, fax 905-546-1125, e-mail mdolovic@mcmaster.ca

TABLE 1
Selected spacers and (valved) holding chambers currently available* in the Canadian marketplace

Device	Manufacturer/Canadian distributor	Internal volume (mL)
Aerosol Cloud Enhancer (ACE)	DHD Healthcare (USA)/VitalAire (Canada)	150
AeroChamber Plus	Trudell Medical International (Canada)	150
E-Z Spacer	Vitalograph (United Kingdom)/ WE Pharmaceuticals Inc (USA)	700
LiteAire	Thayer Medical (USA) /Methapharm Inc (Canada)	160
OptiChamber	Respironics Inc (USA)/Auto Control Medical (Canada)	218
OptiHaler	Respironics Inc (USA)/Auto Control Medical (Canada)	50
PrimeAire	Thayer Medical (USA)/ Methapharm Inc (Canada)	175
SpaceChamber	Medical Developments (Australia)/Alliance Retail Management Group (Canada)	240
Vent-170 Spacer	Nordac Design (Canada)	170
Volumatic	GlaxoSmithKline Canada Inc	750
Vortex	PARI Respiratory Equipment Inc (USA)/PARI (Canada)	194

**As of June 2003*

used during inhalation (4). These factors need to be taken into account when designing protocols to test the performance of these devices.

In many cases, there are little published data to support claims of safety and efficacy other than the information required by the local regulatory body, Health Canada. The only published regulatory guidance that refers specifically to S-HCs was developed over 10 years ago (5) and only cites performance tests at constant flow rates. There is also a lack of guidance concerning the amount and type of information that is provided to health care givers, pharmacists and patients on the device label and the patient instruction insert.

The primary purpose of an S-HC is to aid patient coordination of pMDI actuation and inhalation of the resulting aerosol spray. An important outcome of the S-HC design is the prevention of the ballistic or high-velocity component of the aerosol plume that is emitted from the actuator mouthpiece from depositing into the oropharyngeal cavity. This reduces the amount of active pharmaceutical ingredient swallowed and reduces the possibility of oral candidiasis from inhaled corticosteroids (4). In contrast with simple spacer devices without a valve at the mouthpiece or facemask, an additional function of the holding chambers is the retention of the aerosol for a short time following actuation of the pMDI. This can provide children, the elderly and poorly coordinated patients the opportunity to receive most of the medication if inhalation is slow or delayed (6).

During the mid-1990s, concerns were expressed about the confusion at the pharmacy and physician levels regarding the different inhaler devices that were available without information about their performance. The considerations when choosing a delivery system are numerous, and physicians, health care workers and patients need to be aware of the differences between available marketed devices to help with device selection for the prescribed treatment (7). At the same time, in vitro testing of devices using breathing simulators with realistic variable flow rate patterns demonstrated that holding chambers might not deliver medication when used by infants or small children due to the low inspiratory flow rates generated by these patients (8). Sampling the aerosol at a constant flow rate, as described in other published monographs of test methods, has been the accepted procedure until recently (9). Further in vitro testing revealed that the delivered aerosol from S-HCs may be significantly reduced if the patient delayed inhalation (10). In response to these concerns the Canadian Standards Association called a meeting of stakeholders in 1997 to develop a voluntary consensus standard (Appendix 1). This included the best practices for S-HC storage, performance and use, and guidelines for transparent device and package insert labelling. Finally, a series of in vitro tests to characterize S-HC was developed so that manufacturers could provide data indicative of suitability for the intended patient group(s) obtained under comparable circumstances. Following the establishment of a detailed draft text, public consultation was sought between 2000 and 2001, both within Canada and internationally. The final version of the standard CAN/CSA/Z264.1-02:2002 was published in October 2002 (11). The purpose of the present paper is to provide an overview of the standard, explaining the rationales that shaped its content.

SCOPE

The Inhalant Aerosol Drug Delivery subcommittee agreed to limit the scope of the standard to S-HCs that are used with pMDIs, rather than those with other types of delivery devices, because pMDIs comprise the majority of medical inhalers prescribed. In defining S-HC performance, the focus was on changes brought about by the addition of the S-HC to the pMDI, rather than the function of the pMDI itself or its clinical effects. Data for the pMDI alone are, therefore, required only to provide benchmark values against which to judge the effectiveness of the add-on device. Aspects not considered in the standard were pMDIs with integral spacers, S-HCs used with dry powder inhalers and nebulizers, S-HCs intended for use by patients in the intensive care unit receiving mechanical ventilation, facemask fit (12) and the influence of facemask dead space on S-HC performance (13), and the clinical efficacy and side effects of pMDI medications used with S-HCs.

The decision was made to develop tests that would establish device performance as a complete entity for S-HCs and not to evaluate specific components such as valves. Metrics representing the total dose emitted at the patient interface per actuation of the inhaler and therapeutically relevant subfractions (fine particle dose and extra fine particle dose) were defined to facilitate interpretation of S-HC performance measurements.

S-HC CONSTRUCTION REQUIREMENTS

Not all safety hazards could be anticipated, but the aspects of S-HC design and construction listed in Table 2 were specifically addressed because they are common to almost all devices.

The durability of the S-HC was determined as the resistance to shattering during normal use; resistance to extreme environmental conditions for both use and storage; and resistance to repeated cleaning and maintenance. A series of tests was provided for the manufacturer to evaluate each aspect, depending on the claims made for the device (Table 3).

A simplified aerosol measurement procedure was defined to characterize performance under the durability conditions by measuring the (total) emitted dose ($ED_{S\text{-}HC}$) following a single actuation of a formulation of the tester's choice into the device. The aerosol released at a constant flow rate of 28.3±0.5 L/min, a value close to the average inhalation flow rate for a healthy adult, was collected on a filter placed at the patient interface. $ED_{S\text{-}HC}$ was expressed per actuation. Three repeat measurements on at least three individual S-HC devices were collected for each specified test condition. A common acceptance criterion was developed which specified that the $ED_{S\text{-}HC}$ from each device after each test should not be less than 75% of the mean label claim value reported before implementation of the test conditions, with no individual device in the group having an $ED_{S\text{-}HC}$ of less than 65% of this mean. This specification allowed for variability in unit dose delivery from the pMDI, in addition to any deterioration associated with the S-HC itself. This variability may approach ±20% of the label claim value (based on current regulatory acceptance standards) (14).

TABLE 2
Specific aspects of spacer and (valved) holding chamber (S-HC) construction addressed by the Canadian Standards Association standard CAN/CSA/Z264.1-02:2002

Component	Observation
Any removable component or part that may become dislodged with time	Large enough not to present a choking hazard.
Patient interface (mouthpiece or facemask)	Durable for expected device life or for manufacturer recommended time if designed for replacement in normal use of S-HC.
Valves/valve components	Withstand anticipated environmental/ mechanical conditions of storage and use
Flow indicators	Operate consistently during expected life of device.
Inlet/outlet ports	Prevent accidental attachment of pMDI to mouthpiece (outlet port). Designed to protect S-HC from foreign matter ingress when stored or carried.

pMDI Pressurized metered-dose inhaler

PERFORMANCE CHARACTERIZATION

In vivo testing

Although some believe that the manufacturer should determine, through in vivo testing, that the S-HC can provide clinical benefit, this CSA standard does not define any protocol for clinical trials to demonstrate the efficacy and safety for pMDI drugs prescribed with S-HCs. This decision was arrived at after lengthy discussions within the subcommittee. The consensus was that a single dose comparison of a bronchodilator may be of limted value and that it would not be possible to develop protocols that would compare all types of pMDI formulations and S-HCs or the use of S-HCs in all clinical situations (15-17). Furthermore, it was recognized that two types of S-HCs may have very different in vitro performances and still elicit an equivalent clinical response to a bronchodilator because both may deliver more than sufficient medication to reach the point at which the dose-response curve is insensitive to changes in the delivered dose (17,18). In addition, many published clinical trials testing drugs and inhaler devices are conducted in a laboratory setting where the results do not always translate to what occurs during actual use (17).

In vitro testing

As long as the S-HC delivered approximately the same amount of active pharmaceutical ingredient in the therapeutically relevant size range (ie, less than 4.7 µm aerodynamic diameter [d_{ae}] as that from the pMDI without the add-on device), clinical outcomes would be expected to be similar to those of formulations already evaluated as part of the drug product registration process. Therefore, a key component of in vitro tests was a comparison of the performance of the pMDI with S-HC with that of the inhaler without the add-on device.

TABLE 3
Spacer and (valved) holding chambers (S-HC) durability requirements addressed by Canadian Standards Association standard CAN/CSA/Z264.1-02:2002

Aspect	Comment	Test
Shattering	Components shall be shatterproof.	Drop test from a height of 1.8 m (from mouth to floor).
Environmental conditions	Manufacturer to specify range of conditions for use and storage.	Storage at 60°C/5% RH for one-week (aerosol test at room ambient conditions before and after exposure). Storage at –40°C for one week (aerosol test as above). Cycle for eight days on one-day excursions from –40°C and 60°C/5% RH (aerosol test as above).
Cleaning and maintenance	S-HC designed for proper maintenance over intended lifetime.	Manufacturer to specify washing and disinfection or sterilization procedure.
	S-HC designed for repeated use by a single patient shall remain functional after repeated washing cycles. Those designed for more than one patient shall remain functional after 52 washing cycles AND 20 disinfection or sterilization cycles.	Wash device as many times as expected during intended life (single patient use) or 52 cycles (multiple patient use). Aerosol test before and after repeated washing. Disinfect or sterilize device 20 times. Aerosol test before and after repeated disinfection or sterilization cycles.

RH Relative humidity

TABLE 4
Outcomes from spacer and (valved) holding chamber (S-HC) performance testing at constant flow rate

Parameter	Outcome
R	R for the S-HC with no delay or HC with 2 s delay will be larger than R for the pMDI alone.
F	F should ideally be close to unity for both the extra fine and fine components. A value less than 0.8 indicates significant loss of fine or extra fine particles. F should ideally be zero for the coarse component.
I	I will be greater than unity if the S-HC is effective at all, and will normally be greater than 10.

F In vitro equivalence ratio; HC Holding chamber; I Index of aerosol quality; pMDI Pressurized metered-dose inhaler; R Dose ratio

Constant flow rate testing: The in vitro tests were based on a two-part approach to performance characterization. The first component was measurements at a constant flow rate following a protocol harmonized with that of the United States Pharmacopeia for the measurement of aerosol particle size (9). This involved the use of a multistage cascade impactor to sample and fractionate the aerosol emitted by the device into discrete size ranges between approximately 0.4 μm and 9 μm d_{ae}. Scaling particle size in terms of d_{ae} takes into account the effects of particle shape and density on their ability to reach various parts of the respiratory tract (19,20). The S-HC was attached to the induction port entry to the impactor directly at the patient interface. This requirement was easily met for devices having a mouthpiece, using a coupling that provided a leak-tight seal between the mouthpiece and induction port, while ensuring that the device was aligned on-axis with the induction port entry. The situation was more complex for devices having a facemask because the dead space between the lips of the patient and the adapter for the mask to the S-HC was difficult to standardize because it is dependent on individual facial geometry. For this reason, the subcommittee agreed to specify removing the facemask from the S-HC and using a short connector to secure the device at the mask adapter directly to the induction port.

The approach was to obtain the following metrics which include portions of the emitted dose delivered from the S-HC that have therapeutic relevance (21):

- A coarse particle fraction greater than 4.7 μm d_{ae} that is likely to deposit in the oropharyngeal and laryngeal region and, therefore, be of no clinical benefit to the patient;
- A fine particle fraction less than 4.7 μm d_{ae} that is likely to penetrate and deposit on receptors in the proximal and distal airways; and
- An extra fine particle fraction less than 1.1 μm d_{ae} that is likely to penetrate to the distal airways and alveoli, 18% of which has been reported to be exhaled in healthy volunteers (22).

These directly measured data were obtained for the pMDI alone and for the pMDI with S-HC with no delay following actuation. A further series of measurements with a 2 s delay between actuation and onset of sampling was undertaken specifically for holding chambers, on the basis that these devices, in contrast to spacers, are intended to retain the aerosol for a short time to enable the patient with poor coordination to receive most of the medication. The measurements were made with at least three different formulations representing the main treatment modalities for asthma and chronic obstructive pulmonary disease, namely, bronchodilator, corticosteroid and mast cell stabilizer. This requirement is in harmony with the approach taken by the United States Federal Drug Administration in premarket approval testing for S-HCs (5). At least one of the formulations has to be hydrofluoroalkane-based, in recognition of the transition from chlorofluorocarbon to hydrofluoroalkane propellants with pMDIs.

Three devices were each tested three times to provide a data set comprising nine separate size distributions per group of S-HC. The manufacturer defined the protocol for pretreatment of the S-HC, (eg, washing with ionic detergent to control the influence of surface electrostatic charge [23]) in accordance with the patient instructions for use that are detailed in the package insert. A validation check was made to ensure that the total mass recovery from the pMDI per actuation (material balance) for each measurement was within ±25% of the label claim dose. A protocol was specified for the elimination of outlier data and the calculation of mean values with variance (±1 SD) for each metric.

Using the averaged data, the cumulative mass-weighted size distribution was determined, from which the various mass fractions relating to extra fine, fine and coarse components of the emitted dose were calculated as the ratio (expressed as a percentage) of each portion of the dose compared with the (total) emitted dose. The following parameters which defined the behaviour of the S-HC with each formulation were subsequently derived from these subfractions (19).

- The dose ratio (R value) compares the ratio of fine particle to coarse particle dose for pMDI, pMDI with S-HC (no delay) or pMDI with HC (2 s delay). The R value is not calculated for the extra fine component because this represented less than 5% of the label claim dose for most formulations. The R value should increase from a value close to or less than unity for the pMDI alone to a value in excess of unity with a well-designed S-HC, reflecting the removal of most of the coarse particle component by the device.
- The in vitro equivalence ratio (F value) provides an indication of equivalence or lack of equivalence of the aerosol for depositing in the lower respiratory tract by comparing separately the extra fine, fine and coarse components of the dose delivered from the S-HC with the equivalent values delivered by the pMDI alone.
- The index of aerosol quality (I value) represents the overall effect of the S-HC: the ratio of the R value for the pMDI with the S-HC to the R value for the pMDI alone.

After much discussion, the subcommittee decided to specify limits for these parameters because they are influenced as much by the choice of formulation as by the design of the S-HC. However, the S-HC performance indications provided in Table 4 are for guidance purposes only.

Variable flow rate testing (breathing simulator): The second component of the in vitro performance testing was the determination of the emitted dose with the S-HC connected to a breathing simulator. Spacers were excluded from the part of the test where there was an offset between inhaler actuation and the onset of inhalation (actuation at the onset of exhalation), because the aerosol generated within these devices are expelled during exhalation. However, the emitted dose at the onset of inhalation was determined for this category of devices, because this parameter is a valuable measure of how the spacer performs at variable flow rate under optimum circumstances.

Variable flow rate testing is essential to establish that the inhalation valve of an HC is operating satisfactorily, and provides an indication of how the device might perform in clinical use (24). Five sets of breathing patterns were defined that were deemed representative of neonate, infant, child and adult use (Table 5). These values are similar to data published recently for healthy individuals by Stocks and Hislop (25). Although it is desirable to replicate the durations of inspiration and expiration (inspiration:expiration ratio) per breathing cycle given in Table 5, the subcommittee recognized that some testers may not have access to a computer-driven breathing simulator, so an air flow generator capable of generating a basic sinusoidal wave (inspiration:expiration ratio = 1:1) was thought to be an acceptable alternative. The $ED_{S\text{-}HC}$ was determined by filter collection at the patient interface, with the filter positioned as close as possible to the mouthpiece or mask adapter (mask removed in devices with facemask), thus, simulating clinical use as much as possible. The same indexes were calculated as were done for the measurements at constant flow rate and with three representative test formulations as well.

TABLE 5
Representative breathing patterns for patient categories

	Pediatric			Adult	
Parameter	**Neonate**	**Infant**	**Child**	**Normal 1**	**Normal 2**
Tidal volume (mL)	25	50	155	770	500
Frequency (cycles/min)	40	30	25	12	13
Inspiratory: expiratory ratio	1:3	1:3	1:2	1:2	1:2
Minute volume (mL)	1000	1500	3900	10,000	6000

Data from reference 25

The testing was designed as a two-part procedure (Table 6). In the first part, the measurement was timed so that actuation of the pMDI coincided with the onset of inhalation, thus providing an estimate of the emitted dose that might be inhaled by a fully coordinated patient. In the second part, pMDI actuation was timed to coincide with the onset of exhalation to indicate the dose that might be available to a patient who fails to coordinate pMDI actuation and inhalation properly. The quality parameter (Q) was calculated as the ratio of uncoordinated to coordinated emitted doses. Ideally, the Q value should be one. However, in practice, this parameter is decreased due to the influence of the effects that remove particles from airborne suspensions to the walls of the HC, such as electrostatic charge and gravitational sedimentation. The subcommittee recommended that the Q value normally exceed 0.5 for an effective HC.

MARKING, LABELLING AND INFORMATION TO BE SUPPLIED BY THE MANUFACTURER

Recognizing the need to provide the health care provider, pharmacist and patient an appropriate description of the S-HC, including its correct use and maintenance, the committee focused on the information that is provided on the device package, the S-HC itself and the patient instructions provided in the package insert supplied with the device. The information to be provided was harmonized with the requirements given in Sections 21 to 23 of the (Canadian) Medical Devices Regulations (26). Most of the details are of a routine nature and, therefore, are not considered further in this overview. However, a few aspects are worthy of mention:

- Pharmacists, outpatient clinicians and inpatient hospital users requested that essential information not be discarded with the outside package. The requirement was, therefore, that the package shall not provide any information that is not also provided in the insert.
- Pharmacists requested that the device package provide a means of identifying the patients for whom the product is intended. Patient category could be specified either by age range or patient weight. Alternatively, a list of all patient categories for which the device is deemed inappropriate can be given.
- Clinicians and patients asked that that the device itself be identified with the name and telephone number of a manufacturer-designated and approved contact person who

TABLE 6
In vitro performance metrics from variable flow rate testing by breathing simulator

	Patient category*				
Directly measured parameters	**Neonate**	**Infant**	**Child**	**Adult 1**	**Adult 2**
Part 1 Emitted dose per actuation coincident with onset of inhalation	$ED_{c(neo)}$	$ED_{c(inf)}$	$ED_{c(ch)}$	$ED_{c(ad\text{-}1)}$	$ED_{c(ad\text{-}2)}$
Part 2 Emitted dose per actuation coincident with onset of exhalation	$ED_{uc(neo)}$	$ED_{uc(inf)}$	$ED_{uc(ch)}$	$ED_{uc(ad\text{-}1)}$	$ED_{uc(ad\text{-}2)}$
Calculated parameters					
Quality ratio coordinated to uncoordinated use (holding chambers only)	Q_{neo}	Q_{inf}	Q_{ch}	$Q_{ad\text{-}1}$	$Q_{ad\text{-}2}$

**Breathing patterns defined for each patient category (see Table 5). ad-1 Adult 1; ad-2 Adult 2; c coordinated; ch Child; ED Emitted dose; inf Infant; neo Neonate; Q Quality parameter ($Q=ED_{uc}/ED_{c}$); uc uncoordinated*

would provide help on use and maintenance. This was preferred over giving contact information only on the package or package insert.

- Several representatives suggested that simplified directions for use be provided on the device, together with the words 'clean regularly' or their equivalent, the expiry date (to be determined by the manufacturer) and the statement 'single patient use' or 'do not share'.

- Representatives also asked that attachment points for adjuncts, such as whistle or facemask be indicated to reduce the risk of misassembly. A reference to the package insert for cleaning instructions and the environmental limits for storage and use, as well as a statement to the effect that actual use and storage under extreme conditions may shorten device life.

- For devices with caps, the cap should indicate that it be replaced after use.

APPLICATION OF THE STANDARD

This new Canadian Standards Association standard represents an improvement over previous standards and regulatory guidances for manufacturers of S-HCs that focus mostly on device performance. This goal was achieved by specifying, in detail, requirements for the construction, storage and maintenance of the device, as well as its packaging and presentation to the health care provider, pharmacist and patient. The package of in vitro tests has also been developed with the intention of evaluating important device-related attributes, such as the effect of a delay between pMDI operation and the onset of inhalation for holding chambers, rather than only quantifying the effect that the device has on the underlying pMDI performance. In particular, the use of breathing simulation as a means of providing indicative S-HC performance when used by the patient group(s) for which the device is intended represents a significant advance in testing methodology. The previously existing methods require only that the aerosol emitted at pMDI actuation be sampled at constant flow rate. This type of measurement cannot evaluate inhalation (and exhalation) valve function properly.

At present, this standard is voluntary. Its development was driven by the desire of manufacturers of S-HCs to provide evidence of device safety and efficacy above and beyond that already required by the regulatory authority, and partly in response to requests for more complete information about these devices by advocates for health care providers, pharmacists and patients. The additional work required to achieve compliance is considerable, and represents a significant investment on behalf of manufacturers. Its future adoption will, therefore, depend on how valuable this additional information is perceived to be by user groups. At present, there are no plans for the standard to be made mandatory by the Canadian regulatory authority.

APPENDIX 1
Members of the Inhalation Aerosol Drug Delivery Subcommittee (Z264.1)

M Dolovich (Chair), McMaster University/International Society for Aerosols and Medicine, Hamilton, Ontario

J Baleshta, Nordac Design Inc, Waterloo, Ontario

H Burnett, Inspired Medical Products Inc (Medic-Aid), Charlottesville, Virginia, USA

Z Chad, Canadian Society of Allergy and Clinical Immunology, Ottawa, Ontario

K Chapman, Canadian Network for Asthma Care, North York, Ontario; Canadian Thoracic Society, Ottawa, Ontario

T D'Urzo, College of Family Physicians of Canada, Mississauga, Ontario

S Dunnington, Canadian Society for Respiratory Therapists, Ottawa, Ontario

B Dzyngel, Boehringer Ingelheim (Canada) Ltd, Burlington, Ontario

C Haromy, Asthma Society of Canada, Toronto, Ontario

R Hefford, McArthur Medical Sales Inc, Rockton, Ontario

D Hughes, Canadian representative, US Pharmacopeia, Ottawa, Ontario

D Johnson, GlaxoSmithKline (Canada) Inc, Mississauga, Ontario

A Kenney, Allergy/Asthma Information Association, Toronto, Ontario

L Larsen, Canadian Home Care Association, Ottawa, Ontario

L Lindsay, Ontario Home Respiratory Services Association, Toronto, Ontario

V Migounov, 3M Canada Co, London, Ontario

J Mitchell, Trudell Medical International, London, Ontario

P Murphy, AstraZeneca (Canada) Inc, Mississauga, Ontario

B Schneider, The Lung Association, Ontario office, Toronto, Ontario

A Sinclair, Health Canada, Ottawa, Ontario

M Spino, M Berger, Canadian Drug Manufacturers Association, Toronto, Ontario

K Vallent, PARI Respiratory Equipment Inc, Midlothian, Virginia, USA

B Wells, National Association of Pharmacy Regulatory Authorities, Ottawa, Ontario

J Kraegel (Administrator), CSA International, Mississauga, Ontario

REFERENCES

1. National Institutes of Health, National Heart, Lung and Blood Institute. Guidelines for the Diagnosis and Management of Asthma (publication 97-4051). Bethesda: National Institute of Health, 1997.
2. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS, GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization global initiative for chronic obstructive lung disease (GOLD): Executive summary. Respir Care 2001;46:798-825.
3. Dolovich M. Changing delivery methods for obstructive lung diseases. Curr Opin Pulmon Med 1997;3:177-89.
4. Dolovich MB, MacIntyre NR, Andersen P, et al. Consensus statement: Aerosols and delivery devices. American Association of Respiratory Care. Respir Care 2000;45:589-96. Erratum in: 2000;45:1416
5. Federal Drug Administration. Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators. Center for Devices and Radiological Health. Rockville: Federal Drug Administration, 1993.
6. Dolovich MB. Lung dose, distribution and clinical response to therapeutic aerosols. Aerosol Sci Technol 1993;18:230-40.
7. Pederson, S. Inhalers and nebulizers: Which to choose and why. Respir Med 1996;90:69-77.
8. Mitchell JP, Nagel MW. In vitro performance testing of three small volume holding chambers under conditions that correspond with use by infants and small children. J Aerosol Med 1997;10:341-9.
9. United States Pharmacopeia and the National Formulary (USP 26-NF21). Physical tests and determinations: Aerosols. Rockville: United States Pharmacopeia, 2003:2105-23.
10. Barry PW, O'Callaghan C. The effect of delay, multiple actuations and spacer static charge on the in vitro delivery of budesonide from the Nebuhaler. Br J Clin Pharmacol 1995;40:76-8.
11. Canadian Standards Association. Spacers and Holding Chambers for Use with Metered-Dose Inhalers. Z264.1-02. Mississauga: Canadian Standards Association, 2002.

12. Amirav I, Newhouse MT. Aerosol therapy with valved holding chambers in young children: Importance of the facemask seal. Pediatrics 2001:108:389-94.
13. Everard ML, Clark AR, Milner AD. Drug delivery from holding chambers with attached facemask. Arch Dis Child 1992;67:580-5.
14. United States Federal Drug Administration (FDA). Draft Guidance: Metered Dose Inhaler (pMDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing and Controls Documentation. Docket 98D-0997. Rockville: United States Federal Drug Administration, 1998.
15. Dolovich MB. Characterization of medical aerosols: Physical and clinical requirements for new inhalers. Aerosol Sci Technol 1995;22:392-9.
16. British Thoracic Society; Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. Thorax 2003;58(Suppl 1):i1-94.
17. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: ACCP/ACAAI evidence-base guidelines. Chest 2004. In press.
18. Parameswaran K, Leigh R, O'Byrne PM, et al. Clinical models to compare the safety and efficacy of inhaled corticosteroids in patients with asthma. Can Respir J 2003;10:27-34.
19 Dolovich M. Aerosols. In: Barnes PJ, Grunstein MM, Leff AR, Woolcock AJ, eds. Asthma. Philadelphia: Lippincott-Raven, 1997:1349-66.
20. Mitchell JP, Nagel MW. Cascade impactors for the size characterization of aerosols from medical inhalers: Their uses and limitations. J Aerosol Med 2003;16:341-77.
21. Dolovich MB. Aerosol delivery devices and airways/lung deposition. In: Schleimer RP, O'Byrne P, Szeffler S, Brattsand R, eds. Inhaled Steroids in Asthma. New York: Marcel Dekker Inc, 2001:169-210.
22. Leach C. Enhancing drug delivery through reformulating MDIs with HFA propellants – Drug deposition and its effect on preclinical programs. In: Dalby RN, Byron PR, Farr SJ, eds. Respiratory Drug Delivery V. Buffalo Grove: Interpharm Press, 1996:133-44.
23. Pierart F, Wildhaber JH, Vrancken I, Devadason SG, Le Souef PN. Washing plastic spacers in household detergent reduces electrostatic charge and greatly improves delivery. Eur Respir J 1999;13:673-8.
24. Mitchell JP, Nagel MW. Spacer and holding chamber testing in vitro: A critical analysis with examples. In: Dalby RN, Byron PR, Farr SJ, Peart J, eds. Respiratory Drug Delivery-VII. Raleigh: Serentec Press Inc, 2000:265-73.
25. Stocks J, Hislop AA. Structure and function of the respiratory system. In: Bisgaard H, O'Callaghan C, Smaldone GC, eds. Drug Delivery to the Lung. New York: Marcel Dekker Inc, 2002:47-104.
26. Government of Canada. Medical Device Regulations, SOR 98-282. Ottawa: Government of Canada, 1998.