From the author:

G.F. Sterrazza Papa and co-workers raise valid concerns regarding excessive radiation exposure from chest computed tomography (CCT), which is an area of growing interest for both the medical community and the general public. It is correctly pointed out that multiple scans may mean a significantly increased lifetime attributable risk of cancer when estimated from prior studies of atomic bomb survivors and workers in the nuclear industry [1]. However, it would be remiss to not point out that the risk of cancer from a CCT is not particularly daunting in adults aged >50 yrs with <0.02% lifetime attributable risk per abdominal CT; this is comparable in radiation exposure to our institutions CT pulmonary angiography and less than our non-contrast CCT. As the PORT study found that 74.6% of 1,343 in-patients were aged >50 yrs, it seems likely that CCT would be a fairly safe modality in the majority of hospitalised pneumonia patients [2]. It must be kept in mind that radiation exposure is primarily of concern in younger patients, particularly those aged <20 yrs, where ultrasound is already recommended by the British Thoracic Society [3].

Regardless of the probably negligible cancer risk attributable to radiation exposure in the majority of elderly pneumonia patients, the indiscriminant use of CCT in the assessment of parapneumonic pleural effusion would neither be medically wise nor a judicious use of medical resources. Other techniques such as ultrasound provide a radiation free and readily accessible alternative. It was not our intention to suggest that CCT should replace other means of assessing a pleural effusion. However, whether for good or bad the use of CCT in the USA has increased from 20 million scans per year in 1995 to 62 million by 2005 [1]. As our paper demonstrated, 40% of our admitted pneumonia patients received CCT (mostly CT pulmonary angiography), not for pleural effusion assessment but for the initial evaluation of hypoxia and exclusion of pulmonary embolism while in the emergency room [4]. We think it is important to clarify that the intent of our article was to provide a way to assess the need for thoracentesis when a CCT was already obtained in order to expedite patient care and reduce the cost and radiation exposure of additional testing, and is not suggesting that CCT should become the first line means of assessing parapneumonic pleural effusions.

B.K. Moffett

Correspondence: B.K. Moffett, Dept of Internal Medicine, University of Louisville School of Medicine, 800 Zorn Avenue, Louisville, 40206, KY, USA. E-mail: bryan.moffett@va.gov

Statement of Interest: None declared.

REFERENCES

1 Brenner DJ, Hall EJ. Computed tomography – an increasing source of radiation exposure. *N Engl J Med* 2007; 357: 2277–2284.
2 Fine MJ, Auble TE, Yealy DM, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336: 243–250.
3 Balfour-Lynn IM, Abrahamson E, Cohen G, *et al.* BTS guidelines for the management of pleural infection in children. *Thorax* 2005; 60: Suppl. 1, i1–i21.
4 Moffett BK, Panchabhai TS, Anaya E, *et al.* Computed tomography measurements of parapneumonic effusion indicative of thoracentesis. *Eur Respir J* 2011; 38: 1406–1411.

DOI: 10.1183/09031936.00000812

What the pulmonary specialist should know about the new inhalation therapies

To the Editors:

In the recent report of the European Respiratory Society/International Society for Aerosols in Medicine Task Force [1], the authors correctly identify the need to prescribe spacers (sometimes termed valved holding chambers (VHCs) when an inhalation valve is present) to medication delivered from pressurised metered-dose inhalers (pMDIs). Although they mention that some pMDI products are licensed for use with a particular spacer, they have failed to point out that each pMDI–spacer combination should be treated as a unique system.

In 2008, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) published a recommendation that for inhaled corticosteroids (ICSs), ''Spacers should not be regarded as interchangeable: patients who use a spacer with their inhaler should use the spacer device named in the Summary of Product Characteristics'' [2]. This guidance further stipulates ''Patients whose asthma is well-controlled and who are using a spacer should always use the same type of spacer and not switch between spacers. Different spacers may deliver different amounts of inhaled corticosteroid, which may have implications for both safety and efficacy'' [2].

The following year, the European Medicines Agency (EMA) set out the requirements concerning clinical documentation for orally inhaled products (OIPs) for use in the treatment of asthma and chronic obstructive pulmonary disease [3]. This European-wide guidance specifies, ''When all data collected in the development programme are based on the product administered *via* a pMDI together with one or more specific, characterised spacers, the product can be authorised subsequently for use only if used with the specific named spacer(s).'' Shortly after publication of this guidance, DISSANAYAKE [4] (formerly a Medical Assessor at the MHRA) provided an interpretation of the EMA guidance as follows: ''…given that a

generic and reference pMDI should be interchangeable and given the importance of spacer [VHC] use particularly in children, the failure to provide either *in vitro* or *in vivo* spacer [VHC] data confirming equivalence would generally preclude regulatory approval of the generic product.''

By definition, this recommendation from the drug product-regulating agencies appears to preclude the concept of a spacer without evidence of pMDI compatibility within the countries of the European Union. This position is further supported by the very recent recommendation of BLAKE *et al.* [5]: ''VHCs are not interchangeable, as differences in drug delivery to the lung may occur'' and ''clinicians and pharmacists should be educated not to interchange VHCs once a child is stable on a particular ICS dose and VHC combination.''

The problem concerning the prescription of spacers/VHCs without evidence of pMDI compatibility has arisen in Europe because such products have the lowest safety classification as medical devices. Since spacers/VHCs need not be sterile nor do they measure the dose of drug administered, all manufacturers have to do is to ''self-declare'' compliance to the Medical Devices Directive (MDD) for class 1 devices by means of a Declaration of Conformity. They may then apply the mandatory CE mark directly without further intervention. It is important to note that the purpose of any clinical evaluation that might be undertaken to meet the essential requirements of the MDD is to demonstrate that the device has been designed and manufactured that, when used for the intended purpose, will not compromise the clinical condition or the safety of patients [6]. As such, the evaluation of class I devices does not necessarily mean that a clinical investigation for efficacy and safety takes place, so that the performance of the spacer/VHC need not, therefore, be demonstrated to be pMDI-compatible.

There is abundant published evidence that each pMDI–spacer/VHC is a unique inhaled medication delivery system, from *in vitro* testing of different spacer/VHCs with the same pMDI product and from different pMDI products used with the same spacer/VHC. The clinical evidence for uniqueness with ICSs is less clear [7].

Given the weight of evidence supporting the current regulatory position from the standpoint of the pMDI as the prime drug delivery vehicle, I propose this additional recommendation to the list provided on page 1321 of [1]: ''know that each pMDI–spacer is a unique system, and prescribe the spacer named in the Summary of Product Characteristics (where specified by name). In cases where it is not specified in the Summary of Product Characteristics, a different spacer should not be substituted from what is specified by the recommending clinician''.

J.P. Mitchell

Correspondence: J.P. Mitchell, Trudell Medical International, 725 Third Street, London, ON, Canada. E-mail: jmitchell@trudellmed.com

Statement of Interest: A statement of interest for J.P. Mitchell can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

REFERENCES

1 Laube BL, Janssens HM, de Jongh FHC, *et al.* What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J* 2011; 37: 1308–1331.
2 Medicines and Healthcare Products Regulatory Agency. Inhaled products that contain corticosteroids. London, MHRA, 2008.
3 European Medicines Agency. Requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in adults and for use in the treatment of asthma in children and adolescents. CPMP/EWP/4151/00 Rev. 1. London, EMA, 2009.
4 Dissanayake S. Application of the EU guidelines for pharmacokinetic studies of locally acting orally inhaled drug products. *Respir Drug Deliv* 2010; 1: 293–304.
5 Blake K, Mehta R, Spencer T, *et al.* Bioavailability of inhaled fluticasone propionate *via* chambers/masks in young children. *Eur Respir J* 2012; 39: 97–103.
6 European Parliament. Directive 2007/47/EC of the European Parliament and of the Council of Ministers: Council Directive 93/42/EEC concerning medical devices. *Off J Eur Union* 2007; L247: 21–55.
7 Dolovich MB, Ahrens RC, Hess DR, *et al.* Device selection and outcomes of aerosol therapy: evidence-based guidelines. *Chest* 2005; 127: 335–371.

DOI: 10.1183/09031936.00210911

From the authors:

The European Respiratory Society/International Society of Aerosols in Medicine Task Force thanks J.P. Mitchell for his comments. We agree with his point that the pressurised metered-dose inhaler (pMDI) and spacer, or valved holding chamber (VHC), form a unique system. In the consensus statement [1], we state that ''changing the spacer in effect represents a change in the delivery system''. We also agree that a different spacer or VHC should not be substituted from that specified by the recommending clinician. We also agree that there can be significant differences in drug output with various commercially available spacers and this may have implications for efficacy, especially with inhaled corticosteroids (ICS) [2]. For this reason, our consensus statement states that ''with a change in spacer device, regular monitoring and titration of the ICS dose to the lowest effective dose is advised''. However, a clinician may not always choose to prescribe the VHC that is named in the Summary of Product Characteristics (SPC). This may be because different VHCs have been shown to be clinically effective with the same pMDI [3, 4], implying that there are different choices for an effective VHC.

There are also differences between countries, since the choices for VHCs in a given country depend on their availability. This means that SPCs may differ between countries. For instance, the fluticasone pMDI is recommended to be used with the Volumatic or the Babyhaler (both GlaxoSmithKline, Brentford, UK) in the Netherlands, but with the Volumatic or the Aerochamber (Trudell Medical International, London, ON, Canada) in the USA. Thus, the importance of the recommendation of the SPC may be relative to an individual country. In addition, because of cost, no VHCs may be available in some developing countries. In those countries, household items such