

# The Role of the MDI and DPI in Pediatric Patients: “Children Are Not Just Miniature Adults”

Richard C Ahrens MD

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### Summary

**Metered-dose inhalers (MDIs) and dry powder inhalers play an important role in the treatment of asthma in children of all ages. Yet these devices, which were originally developed for use in adults, interact differently with children. Through childhood there are progressive changes in pharmacokinetic handling and pharmacodynamic effects of inhaled antiasthmatic drugs, in the efficiency and distribution of aerosolized drugs in the respiratory tract, and in the patient’s ability to successfully use aerosol devices. This, in turn, produces changes in potential for producing efficacy and adverse effects, and in the balance between risk and benefit. These differences from adults are greatest for children under 4–5 years of age, who are unable to use DPIs or unassisted MDIs, and who therefore must rely on nebulizers and MDIs with valved holding chambers for inhaled drug delivery. Unfortunately, there are no drugs approved for delivery via MDI (with holding chamber) in children under 4 years of age, and there are insufficient data to ensure that many of the available drug-MDI-holding-chamber combinations are both safe and effective. In particular, the potential for effects of inhaled corticosteroids on growth are insufficiently studied in this age group and remains a concern. It is likely that the risk of adverse effects on growth are different for each of the many possible MDI/valved-holding-chamber combinations. Key words: metered-dose inhaler, MDI, dry-powder inhaler, DPI, inhaled drug, asthma drug delivery, child. [Respir Care 2005;50(10):1323–1328. © 2005 Daedalus Enterprises]**

## Introduction

Aerosol drug delivery plays an important role in the medical treatment of children in multiple settings, includ-

ing management of lung disease of prematurity, bronchopulmonary dysplasia, viral bronchiolitis and croup, cystic fibrosis, and asthma. Metered-dose inhaler (MDI) and dry powder inhaler (DPI) drug formulations play a particularly important role in the treatment of children with asthma, the most common lung disease of childhood. Yet MDIs and DPIs were originally developed and marketed for use by adults, and their adaptation for use with children has been less than perfect. The purpose of this paper is to review the differences between children and adults that can affect aerosol drug delivery to children, to discuss the quality of clinical evidence supporting the safety and efficacy of use of MDI and DPI formulations in children of various ages, and to address practical issues that affect the choice of aerosol therapy in the clinical setting.

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Richard C Ahrens MD is affiliated with the Department of Pediatrics, Carver College of Medicine, University of Iowa, Iowa City, Iowa.

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Correspondence: Richard C Ahrens MD, Department of Pediatrics, 200 Hawkins Drive, University of Iowa, Iowa City IA 52242. E-mail: richard-ahrens@uiowa.edu.

### Factors That Affect Aerosol Treatment in Children

“Children are not just miniature adults.” This truism has long been the justification for the existence of the field of pediatrics and refers to the progressive changes in anatomy, physiology, potential disease processes, and pathophysiology that go on as the child grows from the newborn period through to adulthood. The resulting differences between the child and adult can profoundly affect the medical treatment of the pediatric patient. This includes how the child interacts with and responds to aerosol treatment.

Notable factors that can affect the efficacy, safety, and benefit-risk relationship of inhaled drugs are diagrammed in Figure 1. For inhaled  $\beta$  agonists, the most important issue is delivering a sufficient amount of the drug to the lung to provide efficacy. Acute, dose-related adverse effects (skeletal muscle tremor, modest increases in heart rate, and reduced potassium and increased glucose levels) do not appear to be important safety concerns in pediatric patients,<sup>1</sup> although overreliance on daily use of inhaled short-acting  $\beta$  agonists can be. For inhaled corticosteroids, both ensuring efficacy and avoiding potential adverse effects related to long-term systemic corticosteroid exposure are important issues.<sup>1-3</sup>

For each of the steps diagrammed in Figure 1, there are potential differences between pediatric age groups and adults. Generally, a smaller percentage of the delivered dose is deposited in the lungs of a pediatric patient than in an adult (the younger the child, the smaller the percent deposited).<sup>4</sup> This appears to be due to multiple factors, including smaller airway caliber throughout the child’s respiratory tract, smaller tidal volume, and lower inspiratory flow rate. However, the magnitude of difference between the adult and the child is highly dependent on the specific drug-device system that is used to deliver the aerosol.<sup>5</sup> With some formulations, oropharyngeal deposition is higher in younger patients.<sup>6</sup>

The amount of drug deposited in the lung and oropharynx determines systemic exposure to corticosteroid and, therefore, the potential for adverse systemic effects. The quantity of drug absorbed in the systemic circulation is the sum of that derived from drug deposited in the lung (most of which appears to be absorbed), and that absorbed from the gastrointestinal tract in active form.<sup>2</sup> The latter depends on the amount deposited in the oropharynx (subsequently swallowed) and on the fraction of that drug that escapes inactivation by first-pass metabolism in the gastrointestinal tract and liver. With inhaled corticosteroids this fraction ranges from less than 1% (eg, fluticasone and mometasone<sup>7</sup>) to 30–50% (eg, beclomethasone<sup>8</sup>). Once absorbed, drug is subject to distribution and clearance from the systemic circulation. There can be substantial differences in these pharmacokinetics between children and adults. Children can have a greater volume of distribution

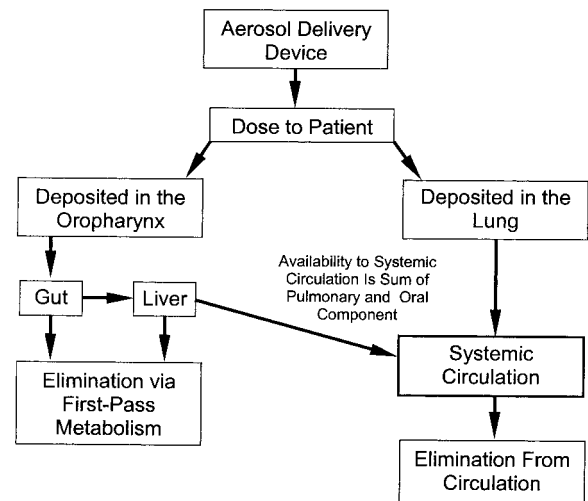


Fig. 1. Factors that determine systemic drug exposure following inhalation of a therapeutic aerosol.

and rate of clearance, and a shorter half-life.<sup>6</sup> The pharmacodynamic effects of inhaled corticosteroids are also different. In adults, important adverse effects include thinning of the skin and decreasing bone density. In pediatric patients, potential effects on the growth and bone density are of greatest concern. Finally, there are the obvious differences in cognitive ability between the younger children and older children and adults. Notably, it is clear that children under 4–5 years of age cannot effectively use a DPI or an unassisted MDI.

### Levels of Evidence Available to Support the Clinical Use of Drugs in Pediatric Patients

The amount of evidence available to support the safe and effective use of drugs in pediatric patients is highly affected by the drug-approval process. The highest level of evidence is generally associated with formulations that have been approved for specific indications and specific age groups. Food and Drug Administration (FDA) approval for adolescents and adults requires 2 adequately designed and well-controlled clinical trials that clearly document safety and efficacy. FDA approval has been obtained for patients  $\geq 12$  years old for virtually all inhaled  $\beta$  agonist and corticosteroid formulations (Fig. 2). A step down from the level of assurance that FDA approval provides is off-label use (ie, use in absence of FDA approval for the specific indication and age group) but for which there is adequate published data supporting safety and efficacy. At the lowest level of evidence, off-label use can occur despite an absence of sufficient clinical trial data to clearly document safety and efficacy. Clinicians who care for children are all too often faced with the latter situations, and forced to decide whether to use a drug in ab-

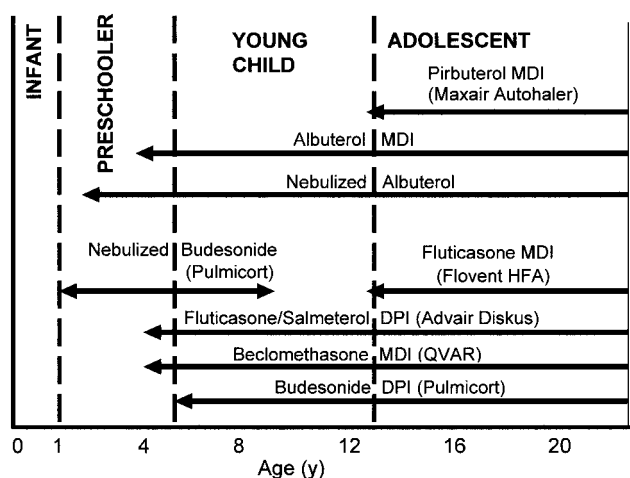


Fig. 2. Approval of inhaled corticosteroids and  $\beta$  agonists as a function of patient age.

sence of a clear picture of its risks versus benefits.<sup>9</sup> The younger the patient, the more likely this is to be true. Using the drug may expose the patient to an uncertain level of risk. Avoiding its use may deny the patient a potentially important treatment for which there may be no suitable alternative. Historically, economic realities have created this situation. For many drugs (including most formulations used to treat asthma), the largest market is among the adult population. Once approval is obtained for adults, the cost of additional studies to document safety and efficacy in younger patients can meet or exceed the potential profits to be made by obtaining FDA approval for marketing the product for use in those younger patients. To deal with this problem, the “pediatric rule” has been put in place to provide an additional economic incentive to pharmaceutical companies to carry out studies with pediatric age groups.<sup>9</sup> The incentive is an additional period of marketing exclusivity that extends the time before generic formulations of the product can be marketed. Since this can be a substantial profit motive, it certainly has helped to increase the number of studies done with pediatric patients. However, some age groups, particularly the very youngest children, remain inadequately studied.

#### MDI and DPI Use With Adolescents (13–18 years old)

The 13–18-years-old age group is most similar to adults, and the full range of adult MDI and DPI options is generally approved and available. Adolescents have pharmacokinetics and pharmacodynamics similar to adults. For inhaled  $\beta$  agonists and inhaled corticosteroids, FDA-approved indications and a few well-supported off-label uses (eg, emergency-room use of higher-than-approved doses of inhaled  $\beta$  agonists) predominate.<sup>10</sup> There is at least one

notable difference between adolescents and adults. The potential for inhaled corticosteroid growth suppression remains a concern in adolescents, particularly with higher doses of corticosteroids. Fortunately, this age group appears to be far less sensitive to growth suppression than younger patients.<sup>11</sup>

#### MDI and DPI Use With Young Children (5–12 years old)

FDA-approved use of MDI and DPI formulations, as well as some well-supported off-label use, predominates in the 5–12-years-old age group as well. There appear to be at least 2 important differences for MDI and DPI use in this group, relative to adolescents and adults. The first is the ability to successfully use these devices. Proper unassisted MDI use is more likely to be a problem in this age group.<sup>12</sup> For this reason, better asthma control is obtained when the MDI is used with a valved holding chamber or a breath-actuated MDI. Optimally, the holding chamber chosen should be one with sufficient published literature to document its effectiveness (eg, the AeroChamber, OptiChamber, or Vortex). Breath-actuated devices include the DPIs and the automatically actuated MDI. While these devices are internally quite different, in the patient’s hands they function remarkably similarly. To minimize the amount of training and potential confusion in a child in this age group, consider combining breath-actuated MDI  $\beta$  agonist and a DPI corticosteroid when the patient requires both of these classes of drugs. The other important difference is greater potential for an adverse effect on growth with inhaled corticosteroids. While it is widely accepted that inhaled corticosteroids play a pivotal role in the management of asthma, over the last decade some concern has arisen about potential growth effects in this age group. The FDA convened an expert panel advisory meeting in June 1998 to review the data.<sup>13</sup> A small but statistically significant decrease in growth rate (about 1 cm over 12 months) was found in several studies involving different inhaled corticosteroid formulations.<sup>14</sup> Subsequent studies provided reassurance that with the lower, recommended doses this growth-rate reduction does not continue to occur on a year-by-year basis, but appears to be a one-time event during the year that the inhaled corticosteroid is initiated.<sup>15</sup> It is now known that growth suppression is dose-related,<sup>16</sup> predominately occurring at doses above 400  $\mu\text{g}/\text{d}$ . Recommended doses appear to have no effect on the final height most children achieve as they complete the growth process.<sup>17</sup> Although uncommon, growth suppression can also occur in an idiosyncratic manner, even at lower doses.<sup>3</sup> For this reason all pediatric patients receiving inhaled corticosteroids should have their growth rate routinely monitored.

### MDI and DPI Use With Infants and Preschool Patients

Nebulizers, MDIs, and DPIs were all originally developed for use by adolescents and adults. None of these 3 types of aerosol device can be used, without adaptation, with infants and preschool children. Children under 4 years of age lack the understanding to coordinate MDI actuation and inhalation. They cannot provide the coordination or the inspiratory flow rate needed to effectively aerosolize the drug from a DPI. They cannot be relied on to hold the nebulizer mouth piece firmly between their lips for the several minutes it takes to deliver the drug solution or suspension from the nebulizer. The nebulizer must be fitted with a mask that directs aerosol to the child's nose and mouth. Occasionally, this has been developed and tested by the manufacturer (eg, the Pari LC nebulizer, marketed with mask as the Pari Baby). More commonly, a mask originally intended for oxygen delivery is attached to the output port of the nebulizer, or the "blow-by" technique is used. MDIs are adapted by use of a valved holding chamber with an attached mask. With the mask firmly applied to the child's face, drug can be delivered to the lung during tidal-volume breathing. To date, DPIs have not been adapted for use with children under 4 years of age.

The approval process is completely separate for the inhalable drug formulations (contained in MDIs, DPIs, and nebulizer solutions or suspensions) and the aerosol delivery devices (compressors, nebulizers, spacers, and valved holding chambers). Within the FDA, the former is handled by the Center for Drug Evaluation and Research, the latter by the Center for Devices and Radiologic Health. The level of clinical evidence available to the clinician is affected by this.

The only inhaled drugs that are FDA-approved for children under 4 years of age are drug solutions (albuterol, cromolyn, nedocromil) and suspensions (budesonide) intended for nebulization. Consequently, the largest amount of clinical evidence for this age group is available for nebulized drugs. Nebulized budesonide (Pulmicort Respules) is the sole inhaled corticosteroid approved. Well-controlled studies document the potential small effect on growth in the first 12 months of use of this agent, but a good safety record overall.<sup>18</sup> In contrast, no MDI corticosteroids are approved for this age group, and all use is off-label. Published data documenting efficacy and longer-term safety for MDI corticosteroids formulations are quite limited. Multiple FDA-approved brands of albuterol nebulizer solution are available for use in this age group, but no albuterol MDIs have been approved.

FDA approval for nebulizers, air compressors that power nebulizers, and valved holding chambers requires only *in vitro* evidence. Many of these devices have been approved for use with children under 5 years of age. Because they

are not required, clinical trials testing these devices are rarely carried out prior to approval. For a holding chamber, the device must be shown in *in vitro* modeling studies to deliver drug similarly (quantity, particle size) to the properly used, unaided MDI. This must include study of only 3 MDI formulations, one from each of 3 different drug classes. After approval, it is generally not possible for the clinician to learn what MDIs were actually studied during the approval process.

The result of this 2-pronged approval process is what might be referred to as "Chinese-restaurant style" aerosol therapy. The clinician can select an MDI drug formulation from "Column A" and one of many available valved holding chamber devices from "Column B." With a false sense of reassurance, the clinician commonly assumes, "it must work OK: it's FDA approved." In fact, many of the possible drug-formulation/device combinations have not been studied in clinical trials in this (or any) age group, and often have not even been studied in *in vitro* bench tests prior to approval. A similar "Chinese restaurant" situation exists for nebulizers, compressors that power nebulizers, and the drug solutions/suspensions used in them.

The consequences of this situation can substantially affect clinical efficacy in children under 4–5 years of age. Nebulized budesonide has clearly been shown in clinical trials to be effective when delivered via the Pari LC nebulizer. However, *in vitro* studies indicate that many available nebulizer-compressor systems will deliver far less drug to the patient than the Pari LC system used in these trials. Use of one of these suboptimal nebulizer systems clearly puts efficacy at risk. There are also large interactions between specific MDI drug formulations and the holding chamber chosen. Based on *in vitro* studies simulating both child and adult respiratory systems, some MDI/device combinations will deliver considerably less drug to the lung than others.<sup>19</sup>

Another important problem that can affect efficacy of nebulizer and MDI/valved-holding-chamber drug delivery to this age group is that many factors can dramatically reduce the quantity of drug delivered to the patient, thereby compromising efficacy. These have been reviewed in detail by Rubin, as part of this conference.<sup>20</sup> It has been shown that the crying child receives very little drug from either a nebulizer or MDI/valved-holding-chamber system. Static charge on the walls of a plastic valved holding chamber, if not treated with ionic detergents to reduce the charge, can also dramatically reduce the amount of drug delivered to the patient. With both nebulizer and MDI/valved holding chamber, a poor mask seal to the face of the infant or young child also dramatically reduces drug delivery. Children under 1 year of age have rather low tidal volumes, compared to the volume of the valved holding chamber. In *in vitro* systems this has also been shown to dramatically reduce the amount of drug that reaches the



patient.<sup>21</sup> Longer than a few seconds delay between actuating the inhaler into the valved holding chamber and having the patient inhale from the chamber can have a similar effect.

The safety of inhaled corticosteroids is also potentially impacted by the drug-formulation/device combination chosen. Elegant pharmacokinetic studies with children under 5 years of age found that proportionately less nebulized budesonide reaches their lung and systemic circulation, relative to adults, but that these children clear drug from their systemic circulation more rapidly.<sup>6</sup> This combines to produce an area under the plasma-concentration/time curve and an index of total systemic drug exposure that is similar to that in older children or adults who receive the same nominal dose via nebulizer or DPI. This indicates that it is not necessary to reduce the nebulized dose administered to children on a per-kilogram basis. Longer-term safety trials confirming this have been carried out only with children under 5 years old with nebulized budesonide. While these data are reassuring, it is easy to envision other scenarios where a child could get a much larger amount of the drug. A similar proportionate reduction in delivery to the lung has been shown for albuterol delivered via MDI with a detergent-treated valved holding chamber. However, the per kilogram dose received by all children was substantially higher than seen in adults.<sup>5</sup> It is not known if the relationship between area under the plasma-concentration/time curve and adverse systemic effects of corticosteroids is the same for young children as it is for older children and adults. In vitro modeling studies of young children with beclomethasone via chlorofluorocarbon-propelled MDI and the Aerochamber indicate delivery efficiency of only about 5% of the dose to the young child's lung. That is at least 2-fold lower than the quantity delivered to the adult lung with the same MDI. On the other hand, the dose of hydrofluoroalkane-propelled beclomethasone (Qvar) delivered to this model of the young child's lung, using an Aerochamber valved holding chamber, is several-fold greater than seen with chlorofluorocarbon-propelled beclomethasone. Other MDI formulation/device combinations probably fall between these extremes. At least one clinical report indicates marked adrenal suppression in children under 5 years old who had been prescribed fluticasone via chlorofluorocarbon-propelled MDI with Aerochamber and mask.<sup>22</sup> This suggests that some patients, especially those who cooperate and use an efficient MDI-holding chamber system well, may be at substantial risk for adverse effects on growth.

This leaves the clinician prescribing inhaled albuterol and/or an inhaled corticosteroid for young children with a complex and confusing list of choices. I suggest several principles to deal with this situation. First, to ensure efficacy, choose an MDI and holding chamber for which there are sufficient published data indicating that adequate drug

delivery is likely. For valved holding chambers available in the United States, Aerochamber has the most published information available about MDI-formulation/holding-chamber interactions. The Aerochamber appears to work well with most commonly prescribed MDIs. Reassuring published data are also available for the Optichamber and Pari Vortex chamber. If prescribing nebulized budesonide, use the nebulizer system that was used in the clinical trials that established safety and efficacy (the Pari LC nebulizer). Second, provide adequate training of the family concerning the potential pitfalls of aerosol drug delivery to this age group. Third, to minimize the risk of adverse effects, carefully monitor the growth of children in this age group who use any inhaled corticosteroid. Rapidly reduce the dose to the lowest that will maintain asthma control.

### Summary

MDIs and DPIs are important in the treatment of asthma with children of all ages, but MDIs and DPIs were developed for adults and they work differently with children. Through childhood, there are progressive changes in the pharmacokinetic handling and pharmacodynamics of inhaled antiasthmatic drugs, in the efficiency and distribution of aerosolized drugs in the respiratory tract, and in the ability of patients to successfully use aerosol devices. This affects potential efficacy, adverse effects, and the balance between risk and benefit. These differences from adults are greatest among children under 5 years old, who are unable to use DPIs or unassisted MDIs, and who therefore rely on nebulizers and MDIs with valved holding chambers. Unfortunately, there are no drugs approved for MDI/chamber delivery to children under 4 years old, and there are insufficient data to ensure that many of the available drug/MDI/chamber combinations are both safe and effective. In particular, the potential for effects of MDI corticosteroids on growth are insufficiently studied in the under-4 age group, and this remains a concern.

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## Discussion

**Smaldone:** One question that I think will emerge about these devices as they go from old to new is the effect of static charge on spacers. I think a lot of the data is roughly equivalent between pediatric and adult patients. You take a given device, you do some output or deposition measurements, and you find that, when you switch to a pediatric scenario, delivery to the patient appears more or less the same, based on the lung size, deposition shifts, et cetera. That's because we use the same kinds of devices for the pediatric and adult situations. It's just a breathing-pattern issue or deposition issue that affects the dose to the lung.

But when you have an order-of-magnitude shift in device function, such as after static charge is removed, and you supply the device with the same MDI as in the static delivery situation, then I think you have issues about delivery. And this applies primarily to spacers. When you get rid of the static charge, the delivery goes way up, and what will happen with a child in those circumstances, if they have a

clinically acceptable situation using a plastic spacer? The same goes for nebulizers that become much more efficient, but the spacer scenario I think is a done deal. There are multiple vendors that are selling these new ones, and I'm not sure what clinical data there are to show that they're safe.

**Ahrens:** Increased efficiency of delivery certainly could create safety issues, particularly in younger children. Both safety and efficacy have been demonstrated for nebulized budesonide, delivered using the Pari LC nebulizer. In contrast, there is very little clinical data to show that any inhaled-steroid-with-valved-holding-chamber combination is safe for children under 5 years of age. It's a little easier to find limited efficacy studies of holding chambers with that age group, and these show that MDI inhaled steroids work when you choose the right holding chamber, be it with budesonide or fluticasone. So if you avoid the well-known pitfalls of valved holding chambers, such as waiting too long between actuating the inhaler and inhalation, and using more than one puff

in the chamber before inhalation, it will probably be effective. But regarding long-term safety there are virtually no data that go beyond the very limited in vitro deposition studies. When these studies suggest increased efficiency of delivery to young children, concern about systemic adverse effects increases.

**Smaldone:** Should we do ACTH [adrenocorticotropic hormone] tests with children, to make sure that they are not growth-suppressed or something? Switching to a static-free spacer delivers a higher dose. How should I deal with that?

**Ahrens:** ACTH testing is certainly one option. Leslie Hendeles has been studying fluticasone plasma levels to address how much Flovent should be given to younger children via valved holding chamber. He has told me that the results suggest that the area under the time/concentration curve is greater for young children receiving fluticasone via an HFA-propelled MDI with antistatic holding chamber than for adults using MDI alone. Optimally,

we'd like to have a full-scale safety and efficacy trial like those done during the drug-development process. In particular, these studies should address effects on growth. That's not going to happen with only individual investigators working on this. That's only going to happen when a corporate sponsor seriously takes this on.

**Rubin:** The "elephant in the room" for many of us is the kids who would rather ignore us. We could look at studies of  $\beta$  agonists or inhaled corticosteroids that showed that two thirds of the infants at the 2-year age who don't have asthma don't develop asthma, and don't respond to these drugs.

**Ahrens:** The issue I think you're addressing is the use of inhaled corticosteroids to treat exacerbations of asthma triggered by viral respiratory infections. These drugs are clearly important for treating persistent asthma, but there is no clear evidence that they decrease frequency, severity, or duration of viral-induced asthma exacerbations. Probably the most relevant issue to clinicians who treat these kids is the difference between viral exacerbations (for which inhaled steroids—at least in conventional doses—do absolutely nothing) and persistent asthma symptoms that clearly are improved by these drugs. Thus, children with pure virally-induced intermittent asthma (who we all see frequently) get no benefit from inhaled steroids: only potential adverse effects.

Even with those who have persistent symptoms, I think there's a spectrum in the efficiency of delivery and the associated potential adverse effects. Some kids who use the device in ineffective ways, such as struggling and crying during aerosol-delivery, get no effect at all. At the other end of the spectrum, in the same population there could be the patient who is being penalized for using the device correctly and therefore perhaps getting a much larger dose than necessary. The first

child will get no benefit, while the second may have safety issues.

**Rau:** If a new device or a change in a device dramatically increases dose availability, such as with the nonstatic chambers, wouldn't that be caught in the device-approval process? Doesn't there have to be some limit within that process? I think this was the problem with Qvar; approval took a long time because they tremendously improved the fine-particle fraction of the aerosol, so they had to change the dosage to make it equivalent.

**Ahrens:** I think you made a leap there. You went from drug delivery using devices such as valved holding chambers to Qvar, which is a drug/device combination. In that leap you went from approval by the CDRH [Center for Device and Radiologic Health] to approval by the CDER [Center for Drug Evaluation and Research]. That's a huge jump.

When you're talking about device approval from CDRH, absolutely not. Clinical studies of safety and efficacy are not part of that CDRH approval process. It is my understanding that the 510K device-approval process requires only that a holding chamber manufacturer show that its device delivers an adequate amount of drug in *in vitro* studies, with a few selected MDIs. Once the approval is obtained, they don't even have to tell you what MDIs were studied. So in the clinical setting people may be using holding chambers with drugs and MDIs they were never tested with, *in vitro* or *in vivo*, during the approval process.

**Coppolo:**\* According to the 1993 Guidance from CDRH's Reviewer Guidance for Nebulizers, Metered Dose Inhalers, Spacers and Actuators,<sup>1</sup> there are actually 5 therapeutic classes of drug that can be used, but the FDA requires

that each of the 3 drugs chosen come from a separate therapeutic class. The rule is as follows: "For each aerosol delivery device or accessory such as an add-on spacer device, particle size distribution testing must include testing with at least one bronchodilator and one steroid. Particle size distribution testing must include at least 3 different drugs, consisting of bronchodilators, steroids, anti-allergics, mucokinetic agents, or antiviral agents." Cromolyn sodium is an anti-allergic for the purpose of this rule. To the best of my knowledge there are no mucokinetic or antiviral agents approved in MDI form, so you are left with choosing one drug in each of the bronchodilator, steroid, and anti-allergic classes. We were recently told that this rule is still in force.

#### REFERENCE

1. CDRH's Reviewer guidance for nebulizers, metered dose inhalers, spacers and actuators: Docket #784, October 1, 1993. Available at: <http://www.fda.gov/cdrh/ode/784.pdf>. Accessed July 28, 2005.

**Ahrens:** So drug companies need to show that their MDI/drug system delivers drug reliably and to conduct clinical trials demonstrating that it is safe and effective, but they are under no obligation to show that their MDI is safe and effective when used with a holding chamber. Device companies, on the other hand, only need to show that their holding chamber works well *in vitro* with 3 MDIs. They are under no obligation to conduct *clinical trials* on whether their device delivers safe and effective amounts of any particular MDI drug. In my opinion, this system does not serve either the clinician or the patient well. This is particularly true for children under 5 years of age.

**Amato:**<sup>†</sup> Device companies certainly won't get involved financially

\* Dominic Coppolo, Monaghan Medical/Trudell Medical International, Plattsburgh, New York.

<sup>†</sup> Michael T Amato, American Respiratory Care Foundation, Irving, Texas; Monaghan Medical/Trudell Medical International, Syracuse, New York.

in long-term pharmacokinetic or clinical studies. They can leave that up to the pharmaceutical companies. The pharmaceutical companies are reluctant to do those add-on-device/drug combination studies, because their approval process comes under scrutiny. It's a big controversy, so that's why what you had can pass as device companies doing a great deal of in vitro testing, because that is more applicable to a device company that can manage its finances. It's a big controversy, because the clinician is looking for in vivo test data. In your meta-analysis that was published in *Chest*,<sup>1</sup> I think that most of the studies that were looked at were in vitro studies, not in vivo studies, mostly because the companies that are doing in vitro studies can't afford to do long-term in vivo studies.

#### REFERENCE

1. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines. American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest* 2005;127(1):335-371

**Ahrens:** Actually that meta-analysis just looked at in vivo randomized

clinical trials. This showed that, in general, nebulizers MDIs, DPIs, and holding chambers all appear to deliver  $\beta$  agonists safely and effectively, *when used properly*, to older children and adults. That's not to say that the choice of which device is used in a specific patient doesn't matter, because there are indeed differences among patients concerning who can use what device *properly*. Usable data was limited for inhaled steroids and largely absent for the youngest children.

I want to be clear that I am *not* impugning the device companies or pharmaceutical companies. I do understand that there are economic pressures that limit available clinical data. What I am saying, as a clinician, is that the inhaled drug/device approval system's broken in terms of how it serves the under-5 age group.

**Geller:** It's my understanding that the FDA approval for drugs for younger age groups depends mostly on safety and not necessarily on efficacy. If that's true, is that how the Advair Diskus drug/device combination got approved down to age 4?

**Ahrens:** Pediatricians would like full efficacy and safety studies to be done for children, particularly when it

comes to persistent asthma, even down to age 4, but there isn't a lot of pathophysiologic evidence that persistent asthma is tremendously different in younger versus older age groups. At least we need to know that we're treating them safely. In general, as the FDA's pediatric rule is applied, if they can get both safety and efficacy, they'll get it. More commonly, compromises have to be made. The first priority is to know a drug is safe for children. If we can have additional efficacy data as well, then so be it.

**Geller:** I wonder if they look at 4-year-olds' ability to use the device? Now that it's FDA approved, that's an assumption, that 4-year-olds can use it correctly.

**Ahrens:** At least with Pulmicort Turbuhaler, Pedersen's work demonstrated that it's possible to train a reasonable percentage of 4-year-olds to use them well.<sup>1</sup> The Advair Diskus may be similar, but I'm not familiar with data documenting that.

#### REFERENCE

1. Agertoft L, Pedersen S. Importance of training for correct Turbuhaler use in preschool children. *Acta Paediatr* 1998;87(8):842-847.