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## Risks of Long-Acting Beta-Agonists in Achieving Asthma Control

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In early December 2008, the Food and Drug Administration (FDA) held an unusual joint meeting of the Pulmonary–Allergy Drugs Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee to consider the safety of long-acting beta-agonists (LABAs). The meeting is described in detail in a Perspective in this issue of the *Journal* by Kramer,<sup>1</sup> who points out that decision making by the advisers and the FDA was hampered by the lack of data about the safety of LABAs.

LABAs, which are administered by inhalation, act by effecting prolonged stimulation of the  $\beta_2$ -adrenergic receptor. They were introduced into the worldwide pulmonary market in the early 1990s and approved for use in the United States in 1994. As active pulmonary physicians, we can attest to their effectiveness. In clinical trials<sup>2,3</sup> and in individual encounters, most patients with asthma who use these medications have improved lung function, and many have diminished symptoms. When LABAs are used together with inhaled corticosteroids, the combination reduces severe asthma exacerbations.<sup>3,4</sup> No one is questioning whether these drugs provide therapeutic benefit.

However, since the introduction of LABAs there has been a concern that they may be associated with an enhanced risk of death from asthma. The Salmeterol Multicenter Asthma Research Trial (SMART), conducted to test the safety of the LABA salmeterol, was stopped when an interim analysis showed an enhanced risk of death for patients taking salmeterol as compared with those taking placebo.<sup>5</sup> (In the trial, patients with asthma who were not otherwise taking a LABA were randomly

assigned to a LABA or placebo for 28 weeks of treatment while their usual asthma treatment was continued.) The risk of death associated with salmeterol was about 1 in 700 patient-years of treatment.<sup>6</sup> Many aspects of the design and conduct of SMART have been criticized,<sup>7</sup> but new clinical trials to test the safety of LABAs have not been launched.

At the meeting of the advisory committees, the panels heard the available evidence concerning the safety of LABAs. Unfortunately, very little new evidence on this issue has been accrued in the past 5 years. Despite the potential risks of these drugs, the companies marketing them have not launched trials powered to show their safety. There is widespread agreement that LABAs should never be used as monotherapy for patients with asthma. Current treatment guidelines actively discourage this practice,<sup>8,9</sup> and the FDA advisory committees meeting in December came to a similar conclusion.<sup>1</sup> Recent meta-analyses of all clinical trials comparing the effects of combined treatment with inhaled corticosteroids and LABAs with the use of inhaled corticosteroids alone have shown a small, nonsignificant increase in death from all causes among the patients receiving the combined treatment. Since these events were so infrequent, the authors of these studies have argued that it was not possible to establish or refute the role of LABAs in causing them.<sup>10,11</sup>

In our opinion, because of confounding and misclassification of death, this issue cannot be resolved by epidemiologic studies or further debate: we need additional data. The onus lies with the FDA and the makers of LABAs to design and

implement appropriately designed and powered trials to determine the safety of these medications. We recognize that these studies would need to be very large and would be expensive, but as members of a community of physicians, we must demand that such studies be done, be done soon, and be done correctly. To meet clinical equipoise, the comparison should be between treatment with inhaled corticosteroids alone and inhaled corticosteroids plus LABAs. The studies should also include both pediatric and adult patients.

To date, the makers of these drugs have not undertaken such large safety studies voluntarily; the FDA may have to require it. Although these studies will be expensive, given that the gross sales of these drugs exceeded \$6 billion in 2008, even a trial costing \$250 million would constitute about 2 weeks of gross profits. A pressing need remains for data on the safety of LABAs, as newer, even longer-acting LABAs are being developed to treat asthma. We urge the FDA to require the start of adequately powered, well-designed studies before the end of 2009, the completion of enrollment in a year's time, and the completion of follow-up by the end of the second quarter of 2011. Until then, physicians should continue to use LABAs to treat asthma, but only together with inhaled corticosteroids. In particular, LABAs should be used only in patients for whom other controller medications alone do not provide adequate, rather than optimal, asthma control. We know that LABAs are effective; the data must be gathered to prove they are safe.

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