Demonstration of In Vivo Bioequivalence of a Generic Albuterol Metered-Dose Inhaler to Ventolin*

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Study objective: To use histamine bronchoprovocation and bioassay statistical procedures to evaluate the in vivo bioequivalence of a generic albuterol metered-dose inhaler (MDI).

Design: A randomized, double-blind, balanced, crossover design was used to determine the potency of each generic albuterol MDI actuation relative to Ventolin (Glaxo Wellcome; Research Triangle Park, NC) administration. One treatment was administered on each of 4 study days. A histamine bronchoprovocation procedure was initiated 1.25 h before and 15 min after administration of the study treatment.

Patients: Twenty-four nonsmoking subjects with mild-to-moderate asthma were studied (18 to 65 years of age; FEV1, > 60% of predicted; and provocative concentration of histamine causing a 20% fall in FEV1 [PC20], ≤ 8 mg/mL at screening).

Interventions: One and four actuations (90 and 360 μg, respectively) of the generic MDI and of Ventolin MDI. Placebo inhalers were used to maintain blinding of inhaler and doses.

Measurements and results: The primary outcome variable was histamine PC20 measured after study treatment administration. A significant dose-effect relationship was present (p < 0.0001). Deviation from parallelism of the generic and Ventolin dose-response curves (p = 0.95) and differences in overall mean response between the two formulations (p = 0.68) were not significant. Using Finney 2 x 2 bioassay statistical procedures, we estimated that one actuation of the generic albuterol MDI was equivalent to 1.01 puffs of Ventolin (90% confidence interval, 0.69 to 1.50).

Conclusion: The generic albuterol MDI delivers a quantity of albuterol to the β2-receptor site in the lung that is the bioequivalent to Ventolin. Further, this study reinforces the validity of this statistical methodology for determining in vivo bioequivalence. (CHEST 2000; 117:714–721)

Key words: albuterol; asthma; bronchial provocation tests; histamine

Abbreviations: ANOVA = analysis of variance; CI = confidence interval; FDA = Food and Drug Administration; MDI = metered-dose inhaler; PC20 = provocative concentration of histamine causing a 20% fall in FEV1

Inhaled β-adrenergic drugs currently occupy a central role in asthma management, especially for the relief of acute respiratory symptoms.1 Albuterol is the most commonly used inhaled β-agonist in the United States.2 Although the patent for albuterol expired in 1989, the first generic metered-dose inhaler (MDI) preparation of albuterol was not approved by the US Food and Drug Administration (FDA) until late 1995 (unpublished letter of approval for albuterol inhalation aerosol manufactured by Norton Ltd, to IVAX Corporation [Miami, FL], agent for Norton Ltd [Waterford, Ireland], from the Office of Generic Drugs, Center for Drug Evaluation and Research, US FDA; December 28, 1995 [obtained under the US Freedom of Information Act]). This delay resulted primarily from the lack of an acceptable and valid method for establishing in vivo bioequivalence of the generic albuterol inhaler to the innovator preparation, Ventolin (Glaxo Wellcome; Research Triangle Park, NC).

A number of methodological approaches have
been advocated for the assessment of generic MDI bioequivalence. Plasma pharmacokinetics have been used to compare the total quantity of albuterol delivered to the lung by generic and innovator products.\textsuperscript{3–5} However, the FDA does not consider this method a reliable reflection of the relative quantity of drug delivered to the site of action in the lung (the \( \beta_2 \) biophase).\textsuperscript{6} Gamma scintigraphy also has been used to evaluate the total quantity of MDI drug delivered to the lung. However, this method also fails to directly indicate drug delivery to the lung biophase.\textsuperscript{7} Two inhalers that produce similar plasma concentration-time curves and scintigraphic profiles could, in fact, yield different biophase concentrations and different levels of effect. This would occur if, for example, one MDI delivered more drug to the alveoli and, consequently, less to the small airways than another.

\textit{In vitro} comparisons of aerosol characteristics produced by generic and brand-name MDIs are a useful aspect of the assessment of bioequivalence testing. These assessments are not sufficient, in themselves, to predict \textit{in vivo} drug delivery to the site of action and to ensure clinical bioequivalence of generic inhaled preparations.\textsuperscript{7}

Clinical studies of \( \beta \)-agonist effects in subjects with asthma are necessary to evaluate the bioequivalence of inhaled \( \beta \)-adrenergic preparations. Such trials rely on the measurement of clinically relevant pharmacodynamic responses to albuterol to reflect the relative quantity of drug delivered to the effector compartment in the lung by the generic and innovator preparations. These studies are best viewed as human bioassay experiments rather than as clinical trials of efficacy. Many of these studies have used albuterol-induced bronchodilation as the pharmacodynamic response measured. A common problem with this response is the failure to show a significant dose-response relationship,\textsuperscript{8} which invalidates the results of the bioassay study. In other words, if the study is unable to distinguish different doses of the reference inhaler, it cannot be expected to reliably detect a difference in dose delivered by the test and reference inhalers.\textsuperscript{9}

We previously developed and implemented a clinical bioassay methodology for comparing the efficacy of inhaled \( \beta \)-agonist preparations.\textsuperscript{10–15} We used two dose levels of each of the two inhaler preparations being compared, \( \beta \)-agonist inhibition of methacholine- or histamine-induced bronchospasm as the pharmacodynamic response measured, and Finney \( 2 \times 2 \) bioassay statistical procedures\textsuperscript{9} to estimate the potency of the generic inhaler relative to the innovator inhaler. This statistical method estimates the number of actuations of the innovator (reference or standard) preparation that would yield approximately the same effect as one actuation of the generic (test) preparation. For example, using this methodology, we demonstrated that each actuation of the Proventil (Key Pharmaceuticals; Kenilworth, NJ) albuterol formulation produces effects equivalent to 1.12 actuations of Ventolin with a 95\% confidence interval (CI) of 0.76 to 1.68.\textsuperscript{12}

The purpose of the work presented here was to use this methodology to determine whether the generic MDI albuterol formulation (Zenith Goldline; Baker Norton Pharmaceuticals; Miami, FL) is bioequivalent to Ventolin albuterol MDI.

**Materials and Methods**

**Subjects**

Twenty-four nonsmoking subjects between 18 and 65 years of age (mean age, 30.1 years) were studied. Nine were men and 15 women. All had asthma as defined by the American Thoracic Society\textsuperscript{16} and could consistently perform reproducible spirometry as defined by the American Thoracic Society guidelines.\textsuperscript{17} Subjects were excluded if one or more of the following occurred: an FEV\(_1\) < 60\% of predicted when daily medications were withheld, a provocative concentration of histamine causing a 20\% fall in FEV\(_1\) (PC\(_{20}\)) of > 8.0 mg/mL, a history of other chronic diseases, or a need for a medication that might alter the response to albuterol. Subjects were not permitted to enter the study if they had a history of viral respiratory tract illness or use of oral corticosteroids in the previous 3 months, an emergency department visit or hospitalization in the previous 6 weeks, or a history of life-threatening asthma in the previous 5 years. The protocol was approved by the University of Iowa Human Subjects Review Committee, and each subject signed an informed consent before entry into the study. Of 60 candidates screened, 29 subjects satisfied the entrance criteria and entered the study. Five subjects exited the study after enrollment because of one of the following reasons: unstable asthma, use of prednisone, a positive pregnancy test, prebronchoprovocation FEV\(_1\) values less than the limits specified in the protocol, and a pre-albuterol administration PC\(_{20}\) that was higher than the protocol-specified limits.

**Histamine Bronchoprovocation**

Histamine bronchoprovocation was performed according to a modification of the method of Cockcroft et al.\textsuperscript{18} Spirometry was performed using a Clinical Pulmonary Function Spirometry system (Model MGC-762-015-101; Medical Graphics Corporation; St. Paul, MN). To establish baseline FEV\(_1\), FVC efforts were performed at 1-min intervals until three consecutive FEV\(_1\) values varied by ≤ 0.1 L. The purpose of performing baseline spirometry in this manner was to allow bronchospasm induced by the FVC maneuver itself to become fully established before proceeding with the bronchoprovocation. Histamine bronchoprovocation was not performed if the best of these final three FEV\(_1\) values was < 60\% of predicted. Each bronchoprovocation began with the inhalation of a phosphate-buffered saline solution control aerosol for 2 min. This aerosol was generated using a Wright nebulizer (Boxon Medi-Tech; Montreal, Canada). The airflow through the nebulizer was calibrated to deliver 0.13 to 0.15 mL of solution per minute. Spirometry was performed at 30 s and 90 s after aerosol inhalation. If FEV\(_1\) values varied > 0.1
L. Spirometry was repeated every 30 s until the highest FEV1 value minus the second highest value was ≥ 0.1 L or until 5 min had elapsed since beginning the aerosol inhalation. The highest FEV1 value was used as the saline solution control value. Five minutes after the start of saline solution control aerosol administration, the initial concentration of histamine was administered and spirometry was performed in a similar manner. At 5-min intervals, the concentration of histamine was increased in twofold increments until the FEV1 had decreased by ≥ 20% from the saline solution control. FEV1 or until the maximum concentration of histamine was administered (64 mg/mL). Side effects observed after the higher histamine concentrations (32 and 64 mg/mL) were those given in previous reports (mild headache or flushing of the skin).\(^{18}\)

**Experimental Design**

This study used a randomized, balanced, double-blind crossover design. MDIs studied were Ventolin MDI (90 \(\mu\)g/actuation) and the generic albuterol MDI (90 \(\mu\)g/actuation). One and four actuations of each inhaler were evaluated (Table 1). Blinding was maintained by the use of multiple placebo and active inhalers such that the total number of actuations on each study day was the same (four actuations), although only one puff was taken from each inhaler. A placebo treatment arm was not included in the study design because the estimation of potency of the generic inhaler relative to Ventolin (the primary outcome measure of the study design because the estimation of potency of the generic inhaler relative to Ventolin (the primary outcome measure of the study design) uses the difference in response between doses rather than the difference between active treatments and placebo. In addition, multiple previous studies using this model have shown that little or no placebo effect occurs.\(^{12,14,15,19,20}\) A nurse not involved in data collection administered the study treatment. The subject was blindfolded so that visual identity of the MDI administered was secure.

One treatment was administered on each of four separate study visits. At least 24 h and not > 2 weeks were permitted between study visits. Treatments were balanced across visits using the Latin square method. Each visit began with baseline spirometry and histamine bronchoprovocation. To proceed further with the study visit, a baseline PC20 was required to be within a ninefold range of baseline PC20, from all prior study visits for that subject. A minimum of 1.25 h after completion of the baseline challenge (sufficient time for all subjects to fully recover from the effects of the histamine and for FEV1 to return to within 10% of baseline that day), the test inhaler was administered. MDIs were shaken vigorously and primed in a separate room by actuating the canisters five times over a period of 2 min. Subjects actuated the test MDI immediately after beginning a slow inhalation from functional residual capacity to total lung capacity (< 0.5 L/s). Subjects then held their breath for 10 s and exhaled. A second histamine bronchoprovocation was initiated 15 min after MDI administration. The starting histamine dose was fourfold greater than the baseline PC20 for that visit. This permitted completion of the bronchoprovocation between 30 and 45 min after MDI administration.

Antihistamines were withheld from subjects for 5 days (astemizole, 6 weeks), inhaled \(\beta\)-agonists for 8 h, theophylline for 36 h, and inhaled corticosteroids for 2 h before each study visit. Nonsteroidal anti-inflammatory agents were withheld for 7 days before each study visit, and xanthine-containing foods were withheld for 24 h. No subject received cromolyn within 2 weeks before the study or during it. Subjects were studied at approximately the same time of day at each visit.

**Statistical Analysis**

For each histamine bronchial provocation, the concentration of histamine that would have produced exactly a 20% decrease in FEV1 (PC20) was estimated by interpolation from a plot of logarithmic histamine concentration vs the percentage of decrease in FEV1 from the saline solution control. Finney 2 \(\times\) 2 bioassay analysis procedures\(^{9}\) were used to estimate the potency of the generic MDI relative to the Ventolin MDI and to evaluate established study validity criteria. PC20 values were logarithmically transformed before analysis to meet the equal variance assumption of analysis of variance (ANOVA). The relative potency indicates the number of actuations of the Ventolin MDI estimated to produce effects equal to one actuation of the generic MDI. A 90% CI was calculated for this estimate. The validity criteria, which use ANOVA to determine whether a valid estimation of potency can be made, include the following: (1) the presence of a significant dose-response relationship (regression contrast); (2) the absence of deviation from parallelism of the dose-response curves for the two inhalers (parallelism contrast); and (3) the absence of deviation of the dose-response relationship from linearity (preparations contrast). Because only two doses of each preparation were administered, the linearity of the dose-response relationship could not be assessed. However, even if nonlinearity were present, this would not have affected validity of use of the relative potency to demonstrate bioequivalence. Linearity is not a critical factor affecting study validity when the magnitude of responses to the preparations studied are similar (as would be expected if Ventolin and the generic inhaler were indeed bioequivalent).\(^{9}\)

**RESULTS**

PC20 values measured before the study MDI treatment were not significantly different (\(p = 0.36\)). ANOVA indicated that a significant overall difference between posttreatment PC20 values was present (\(p < 0.001\); Table 2; Fig 1). This was related to a significant dose-response relationship (\(p < 0.0001\)). The parallelism and preparation contrasts were not significant. The estimated potency ratio was 1.01, indicating that each actuation of the generic MDI delivered

**Table 1—Dosing Scheme**

<table>
<thead>
<tr>
<th>Test MDI</th>
<th>Test MDI, Actuations Administered</th>
<th>Placebo, Actuations Administered</th>
<th>Dose of Albuterol Delivered at Mouthpiece, (\mu)g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic MDI, 90 (\mu)g/actuation</td>
<td>1</td>
<td>3</td>
<td>90</td>
</tr>
<tr>
<td>Generic MDI, 90 (\mu)g/actuation</td>
<td>4</td>
<td>0</td>
<td>360</td>
</tr>
<tr>
<td>Ventolin MDI, 90 (\mu)g/actuation</td>
<td>1</td>
<td>3</td>
<td>90</td>
</tr>
<tr>
<td>Ventolin MDI, 90 (\mu)g/actuation</td>
<td>4</td>
<td>0</td>
<td>360</td>
</tr>
</tbody>
</table>
the same quantity of albuterol to the \( \beta_2 \)-receptor biophase in the lung as 1.01 actuations of the Ventolin MDI (90% CI, 0.69 to 1.50). Adverse event profiles for the two MDI preparations were similar, and no serious adverse events occurred.

**Discussion**

Results presented here provide an assessment of the potency per actuation of the generic albuterol inhaler relative to that of the Ventolin inhaler. Each actuation of the generic inhaler is estimated to deliver a quantity of albuterol to the \( \beta_2 \)-receptor biophase in the lung that is equivalent to 1.01 actuations of the Ventolin MDI, with a 90% CI for this estimate of 0.69 to 1.50. Stated another way, this indicates that each actuation of the generic albuterol inhaler delivers significantly more [68% (\( p, 0.05 \)) and significantly more [151% (\( p, 0.05 \))] as much albuterol to the biophase as does one actuation of Ventolin. The fact that the CI lies entirely within the range that the FDA currently accepts for definition of bioequivalence (range, 0.67 to 1.50) provides evidence that the generic albuterol is bioequivalent to Ventolin.

The approach used in this study for assessment of *in vivo* bioequivalence of inhaled albuterol is analogous to that used to evaluate orally administered generic formulations. *In vivo* bioequivalence evaluation for oral agents uses pharmacokinetics to estimate the relative quantity of drug delivered from the GI tract to a relevant biological compartment (the plasma). FDA criteria usually require an oral generic agent to deliver between 80% and 125% as much drug to the plasma as the innovator product. For *in vivo* bioequivalence assessment of inhaled albuterol preparations, the relevant biological compartment is the \( \beta_2 \)-receptor biophase in the lung rather than in the plasma compartment. The measurement methodology used is a biological assay rather than a chemical measurement of drug concentration. The range that the FDA currently accepts for establishment of bioequivalence is somewhat wider (range, 67 to 150%) than is usually required for oral generic drugs. However, the concepts are otherwise analogous.

Use of a bioassay study design is necessary if a clinical study is intended to assess whether a generic inhaled albuterol formulation is bioequivalent to the

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**Table 2—Effect of Albuterol Delivered by Generic and Ventolin MDIs on PC<sub>20</sub> to Histamine<sup>a</sup>**

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Generic MDI 90 µg Pre</th>
<th>Post</th>
<th>Ventolin MDI 90 µg Pre</th>
<th>Post</th>
<th>Generic MDI 360 µg Pre</th>
<th>Post</th>
<th>Ventolin MDI 360 µg Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.21</td>
<td>34.23</td>
<td>6.29</td>
<td>19.69</td>
<td>1.56</td>
<td>14.71</td>
<td>1.72</td>
<td>9.76</td>
</tr>
<tr>
<td>2</td>
<td>0.41</td>
<td>7.58</td>
<td>0.59</td>
<td>16.18</td>
<td>1.40</td>
<td>8.87</td>
<td>1.77</td>
<td>18.06</td>
</tr>
<tr>
<td>3</td>
<td>0.08</td>
<td>0.30</td>
<td>0.10</td>
<td>0.32</td>
<td>0.30</td>
<td>0.97</td>
<td>0.14</td>
<td>0.76</td>
</tr>
<tr>
<td>4</td>
<td>2.21</td>
<td>31.50</td>
<td>3.97</td>
<td>40.05</td>
<td>2.12</td>
<td>25.71</td>
<td>1.85</td>
<td>28.08</td>
</tr>
<tr>
<td>5</td>
<td>0.38</td>
<td>7.54</td>
<td>1.30</td>
<td>28.58</td>
<td>2.26</td>
<td>9.94</td>
<td>2.14</td>
<td>18.16</td>
</tr>
<tr>
<td>6</td>
<td>0.27</td>
<td>0.68</td>
<td>0.22</td>
<td>2.00</td>
<td>0.17</td>
<td>0.74</td>
<td>0.42</td>
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</tr>
<tr>
<td>7</td>
<td>4.96</td>
<td>60.48</td>
<td>2.48</td>
<td>38.91</td>
<td>6.73</td>
<td>25.60</td>
<td>2.37</td>
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<td>8</td>
<td>1.42</td>
<td>25.08</td>
<td>1.19</td>
<td>25.0</td>
<td>1.55</td>
<td>10.92</td>
<td>1.03</td>
<td>34.03</td>
</tr>
<tr>
<td>9</td>
<td>1.53</td>
<td>24.30</td>
<td>2.10</td>
<td>78.20</td>
<td>1.27</td>
<td>17.32</td>
<td>1.06</td>
<td>46.23</td>
</tr>
<tr>
<td>10</td>
<td>2.30</td>
<td>30.61</td>
<td>2.45</td>
<td>163.40</td>
<td>1.09</td>
<td>24.29</td>
<td>2.65</td>
<td>76.88</td>
</tr>
<tr>
<td>11</td>
<td>0.73</td>
<td>9.57</td>
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<td>2.25</td>
<td>8.93</td>
<td>0.53</td>
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<tr>
<td>12</td>
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<td>0.60</td>
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<td>8.92</td>
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<td>0.93</td>
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<tr>
<td>18</td>
<td>8.88</td>
<td>202.95</td>
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<tr>
<td>19</td>
<td>5.45</td>
<td>25.31</td>
<td>4.84</td>
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<td>4.64</td>
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<td>0.68</td>
<td>33.29</td>
</tr>
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<td>24</td>
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<td>0.09</td>
<td>36.74</td>
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<td>13.02</td>
<td>0.19</td>
<td>28.91</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>0.77†</td>
<td>9.78†</td>
<td>0.83‡</td>
<td>10.22‡</td>
<td>20.39†</td>
<td>0.91‡</td>
<td>19.23‡</td>
<td></td>
</tr>
</tbody>
</table>

*Pre = before dosing with study inhaler; Post = after dosing with study inhaler.
†Pretreatment means were not significantly different.
‡Posttreatment means were significantly different (\( p, 0.001 \)). This was entirely because of a significant difference between doses (see text).
standard or reference preparation (Ventolin). In essence, this involves administering more than one dose of at least one of the two formulations being compared so that a dose-response relationship can be established. This dose-response relationship then serves as a standard curve, which is used to translate the response to the generic inhaler into an equivalent dose of the reference formulation. Studies that compare responses to only one dose of each formulation cannot provide this information because no dose-response standard curve can be established. We used a 2 × 2 study design in which two doses of both formulations are administered. This not only provides a more powerful evaluation of the dose-response relationship than administering multiple doses of just the standard formulation, it also provides an opportunity to evaluate whether the dose-response curves are parallel for the two formulations.

Analysis of a bioassay study such as that presented here estimates the potency of the generic (or test) inhaler relative to the reference (or standard inhaler) and places a CI on this estimate. More than one statistical method is available to accomplish this. We used the Finney bioassay statistical procedure. This approach, first introduced by Finney21 and others in the 1940s, is based on ANOVA. As part of the approval process for the generic MDI, the FDA applied an alternative analytic procedure to our data to estimate the potency of the generic albuterol MDI relative to the Ventolin MDI and to determine the associated CI. They constructed a piecewise linear-fit model of the Ventolin dose-response relationship that assumed a linear response between zero actuations (ie, pretreatment PC20 values) and one actuation of Ventolin, and a separate log-linear response between one and four actuations of Ventolin. Using this composite, piecewise-fit model as a standard curve and the response to one actuation of the generic inhaler, they estimated that each actuation of the generic albuterol MDI delivered 0.95 as much albuterol to the biophase as the Ventolin MDI. Bootstrap analysis22 rather than ANOVA then was used to establish a 90% CI around this estimate of 0.69 to 1.40. This approach requires fewer statistical assumptions than does the Finney analysis. The fact that the estimates obtained using bootstrap analysis are nearly the same as those obtained in our analysis using the Finney bioassay statistical procedures is reassuring.

The pharmacodynamic response chosen is also an important factor in the design of a successful bioassay study. The response used must be clinically relevant and must exhibit an albuterol dose-response relationship that is sufficiently steep in the range of doses studied. To be clinically relevant, a pharmacodynamic response must use the same biophase (ie, the same receptor sites in the lung) as is used in clinical treatment. We used the ability of albuterol to protect against bronchospasm induced by histamine bronchoprovocation. This bronchoprotective function of albuterol is clearly an important aspect of the clinical use of this drug (eg, protection against exercise- or cold air-induced bronchospasm). A potential disadvantage of this method is that it requires considerable investigator expertise to perform it accurately and effectively. Albuterol-induced bronchodilation is another suitable pharmacodynamic response in that it mimics clinical use as treatment for bronchospasm that is already present. This response also has been used successfully to establish bioequivalence for an FDA approval of another

![Figure 1](http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21941/ on 06/16/2017)
inhaled generic albuterol preparation (unpublished study report; Sidmak Laboratories, East Hanover, NJ).

Steepness of the inhaled albuterol dose-response relationship associated with a pharmacodynamic outcome is important because this determines whether sufficient statistical power will be present to make a clinically useful assessment of bioequivalence. Albuterol protection against bronchoprovocation was chosen for this study because its dose-response

Figure 2. Top: Relationship between s/b and difference between response to test and Ventolin MDIs. Curved reference lines indicate the expected difference in effect between the test and Ventolin MDIs on PC_{20} if the test MDI was known to deliver exactly 0.5, 0.67, 0.8, 1.0, 1.25, 1.5, and 2.0 times as much albuterol to the β_{2}-receptor biophase in the lung as Ventolin. This expected difference is a function of the value of s/b. Plotted points represent the difference in response to the test albuterol and the Ventolin MDI (± 90% CI) observed in the current study and in four other studies using similar methodology (data for Medisol generic albuterol from unpublished study report; Sidmak Laboratories, East Hanover, NJ). Two hypothetical studies with similar response variability but smaller (study A) and larger (study B) s/b ratios also are plotted (see text for further explanation). Bottom: Estimated potency of test inhaler relative to the Ventolin MDI and its 90% CI calculated by applying Finney bioassay statistical procedures to the studies plotted above. CFC = chlorofluorocarbon.
relationship is steep enough to permit precise estimates of potency of the generic albuterol relative to the standard with as few as 15 to 30 subjects. The statistical power of a given pharmacodynamic response for estimating relative potency is related not only to the slope of the dose-response relationship (commonly symbolized as b) but also to the variability of the response (e.g., standard deviation, symbolized here as s). It is the ratio of these two factors (s/b) that determines the sample size needed to precisely estimate relative potency.9 Stated another way, the slope associated with a pharmacodynamic response only can be judged to be steep or shallow in the way it relates to the variability of that response. The smaller the value of s/b, the fewer the subjects that will be required for a precise estimate of relative potency.

In Figure 2 (top), s/b values obtained from the current study and five similar studies are plotted (x axis) against the observed difference in response between the two preparations being compared (y axis). The difference in response is expressed as effect size (number of observed SDs of the response variable by which the two formulations differ). This approach to expressing differences in response is commonly used in meta-analysis to allow studies with different outcome measures (and therefore different response units) to be combined and analyzed together. In Figure 2, this approach was used to allow studies with different response units (e.g., percentage of change in FEV1 vs PC20) to be plotted on the same graph. The labeled reference lines indicate the magnitude of difference in response between the two inhalers that would be expected if the test MDI delivered 0.5, 0.67, 0.8, 1.0, 1.25, 1.5, or 2.0 times as much albuterol to the lung biophase as the reference inhaler, the Ventolin MDI. To further illustrate the importance of the dose-response slope, two hypothetical studies (A and B) have been included in Figure 2. These two hypothetical studies have the same observed difference between mean responses to test and reference inhaler (equal to zero) and the same size 90% CI around this difference. However, study A has a high value of b relative to s (i.e., a steep slope relative to the variability present) and, therefore, a low value of s/b. This places study A on the left side of the graph in Figure 2, top, where its 90% CI lies well within the range between the 1.25 × as potent and 0.8 × as potent reference lines. Consequently, the 90% CI around the potency of the test inhaler relative to the Ventolin MDI is quite narrow (Fig 2, bottom). Such a study would provide compelling evidence for bioequivalence of the test and reference inhalers. In contrast, study B has a small value of b relative to s (a flat slope relative to the variability present) and, therefore, a large value for s/b. This places study B on the right side of the graph in Figure 2, top, where its 90% CI around the difference in response extends across all the relative potency reference lines (from 0.5 to 2.0 times as potent). The CI around relative potency (Fig 2, bottom) is so broad that it is of little use to the clinician (i.e., it has little power to discriminate differences in albuterol delivered to the lung).

Five of the six real studies plotted in Figure 2 use bronchoprovocation to assess relative potency (i.e., the current study and the studies of the Spiros albuterol dry powder inhaler [Dura Pharmaceuticals; San Diego, CA], Alupent [Boehringer Ingelheim Pharmaceuticals, Inc; Ridgefield, CT], chlorofluorocarbon propelled Proventil, and Maxair MDIs [3M Pharmaceuticals; St. Paul, MN]). Although not as precise as hypothetical study A, these studies do provide clinically useful information. There are many published examples using bronchodilation as the response studied, which, like hypothetical study B, have little ability to discriminate difference in delivered albuterol dose.8 Still, when properly designed and conducted, studies using bronchodilation also can have sufficiently steep dose-response slopes to provide clinically useful assessments of relative potency of the inhaler being compared (e.g., the study of Medisol generic albuterol in Fig 2; unpublished study report; Sidmak Laboratories, East Hanover, NJ).

In summary, we demonstrated that the generic albuterol inhaler produced by Baker Norton Pharmaceuticals meets the FDA established criteria for in vivo bioequivalence to the Ventolin albuterol MDI using a histamine challenge-based clinical bioassay. Methodologies developed for this project may prove useful in evaluating the bioequivalence of new generic inhaled albuterol preparations, as well as assessing the comparability of albuterol delivery to the lung by other inhaled albuterol delivery devices such as non-fluorocarbon-containing MDIs and dry powder inhalers.

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