

# Introduction to the Canadian Scientific Advisory Committee on Respiratory and Allergy Therapies: *In Vivo* Evaluation For Clinical Testing in COPD and Asthma Therapy Using Generics

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## Abstract

**Background:** Health Canada posted a guidance for *in vivo* testing of subsequent market entry (SME) inhaled corticosteroids (ICS) for treatment of asthma and published proceedings regarding SME products for chronic obstructive pulmonary disease (COPD). This manuscript reviews these recommendations and outlines their rationale.

**Methods:** The Scientific Advisory Committee on Respiratory and Allergy Therapies (SAC-RAT) met between 2007 and 2009. The committee reviewed approval processes for SME ICS for asthma treatment and a draft guidance was posted by Health Canada. SAC-RAT also reviewed SME long-acting beta agonists (LABA) and fixed drug dose combinations (FDDC) for COPD treatment.

**Results:** SAC-RAT concluded that measuring airway eosinophils in mild, stable, steroid-naïve, subjects was reproducible and measurable. Study duration could be reduced to only 3 weeks using this inflammatory outcome to establish therapeutic equivalence between SME ICS and Canadian reference product. A placebo limb of the trial was added to establish biological activity of the products. The committee recommended that LABA SME products be tested in a clinically stable, representative population with GOLD stage 2 and/or 3 COPD. There was not agreement regarding the extent of allowed FEV<sub>1</sub> reversibility in this population. The FEV<sub>1</sub> area under the curve (AUC) was recommended as a primary endpoint. For equivalence, both AUC and the shape of the curve (assessed by the peak and trough) over a 12-h period should be different from placebo but similar for the SME and reference products. Secondary endpoints were not recommended.

**Conclusions:** Clinical presentations of asthma and COPD may overlap but prespecified disease phenotypes can separate the populations. ICS therapeutic equivalence can be assessed by reduction in eosinophil counts tested in steroid naïve subjects. Increases in FEV<sub>1</sub> define LABA effects in moderate to severe COPD. When designing trials to assess therapeutic equivalence, the anticipated mechanism of action of the drug should be used to determine outcome measures.

**Key words:** asthma, COPD, generic, metered dose inhaler, inflammation

## Introduction

THE SCIENTIFIC ADVISORY COMMITTEE on Respiratory and Allergy Therapies (SAC-RAT) is a Health Canada committee charged with the development of “standards of evidence” decision making for respiratory and allergy therapies as well as development of clinical and nonclinical guidances to facilitate the assessment of new drugs used to treat allergy

and respiratory disease. The committee met between January 2007 and November 2009 to create industry guidance for subsequent market entry (SME) products for the treatment of asthma or chronic obstructive pulmonary disease (COPD). The committee generated recommendations related to SME inhaled corticosteroids (ICS) for the treatment of asthma, long-acting beta agonists (LABAs) for treatment of COPD, and fixed drug dose (FDDC) combination ICS and LABA also

for the treatment of COPD. This article will review the recommendations, with rationale for these recommendations when possible, for these SME products.

### Considerations for Trial Design of ICS SME Products

Serum levels of a systemically delivered drug can be collected and the concentration over time of the SME can be compared with the reference product to show equivalence. However, this process cannot be used when establishing the therapeutic equivalence of SME ICS products compared with the reference product. The site of beneficial action of inhaled agents such as ICS is at the level of the airways and this determined by a complex interaction of particle characteristics, airflow, and disease pathophysiology. Therefore, circulating blood levels do not necessarily reflect the therapeutic effects of an SME ICS. To date, there is not a validated model to test therapeutic equivalence of SME ICS products to Canadian Reference product.

SAC-RAT members recognized that if reference product had a pediatric indication then any SME ICS product would be used in pediatric populations even if therapeutic equivalence was only established in an adult population. As such pediatric specific issues such as sensitivity to excipients<sup>(1)</sup> must be addressed by any guidance. Also, because spacer devices are recommended for use with metered dose inhalers (MDIs) in pediatrics, the design of any SME MDI must be compatible with existing spacer devices. Spacer compatibility was considered to be both an adult as well as a pediatric concern.

The committee considered requirements for any experimental design of a test of therapeutic equivalence. The committee concluded that any trial should include a placebo limb to establish that the test product actually has a measurable therapeutic effect before considering if the effects were comparable to the reference product. However, the use of a placebo for any extended time period in subjects with persistent asthma actively controlled on ICS raised ethical issues. The committee did not believe that it was acceptable to withhold a proven, efficacious therapy for any extended time period. Discontinuing low-dose ICS therapy in patients with well-controlled asthma has been shown to significantly increase treatment failure compared to continued ICS use.<sup>(2)</sup> This treatment failure occurred despite substituting ICS therapy with a nonsteroid controller medication. It has also been shown that discontinuing ICS in subjects with mild asthma and relying only on short-acting  $\beta$ -agonist rescue medication increased the frequency of exacerbations requiring oral prednisone therapy.<sup>(3)</sup> Therefore, the committee recommended that any trial of therapeutic equivalence should expose subjects to a short duration of placebo therapy and should attempt to choose subjects with a low probability of severe exacerbations while on placebo.

There is a wide range of possible outcomes that could be used to determine therapeutic equivalence. Most commonly pivotal trials for licensing a new product for the treatment of asthma use the forced expired volume in 1 second (FEV<sub>1</sub>) as a primary outcome measurement. However, subjects with asthma have other measurable changes in their physiology or health status that could be used instead. These include measurements of airway inflammation (sputum eosinophil counts,<sup>(4)</sup> sputum cytokine levels,<sup>(5)</sup> or exhaled nitric oxide

(eNO)<sup>(6)</sup> levels). Besides changes in FEV<sub>1</sub>, changes in bronchial hyperreactivity have been used to follow treatment effects in asthma and these are typified by tests such as methacholine challenge.<sup>(7)</sup> Finally, changes in health status measured by disease specific questionnaires (e.g., Asthma Quality of Life Questionnaire<sup>(8)</sup>) have been used as treatment outcomes indicators. SAC-RAT members considered which, if any of these measurements, satisfied their requirements for safety and still were robust and reliable.

### Health Canada Draft Guidance for ICS SME Product Submission

With input from SAC-RAT, Health Canada published a draft guidance for ICS SME products.<sup>(9)</sup> The guidance was intended to assist in filing submissions for SME ICS products with the proviso that this submission would apply only for the indication of the treatment of asthma. The guidance included general SME MDI requirements including submitting complete chemistry, manufacturing, and quality control data. As well, any submission must include the required data outlined within "Guidance For Industry: Pharmaceutical Quality of Inhalation and Nasal Products."<sup>(10)</sup> Finally, there must be evidence of compatibility with existing spacer devices or chambers. The remainder of the guidance focused upon the determination of therapeutic equivalence and safety.

SAC-RAT recommended that an index of airway inflammation should serve as a primary outcome measurement to determine therapeutic equivalence of ICS SME product with the reference product. The rationale for this approach was based upon a growing literature describing the anti-inflammatory effects as the primary mode of action of ICS medications in asthma. Jatakanon et al.<sup>(11)</sup> described a significant reduction in sputum eosinophil counts with low-dose ICS. These subjects all had mild asthma as typified by their requirement for less than one inhalation of rescue medication per day while maintaining good asthma control. These investigators later demonstrated that sputum eosinophil counts showed a dose-response to ICS.<sup>(12)</sup> These were again subjects with mild asthma and they showed the greatest absolute change in eosinophil counts with the lowest dose of ICS tested. Although ICS are not direct bronchodilators, this study also noted a significant improvement in measurement of airflow (FEV<sub>1</sub> and peak expiratory flows). However, improvements of FEV<sub>1</sub> are not uniformly noted in trials of ICS in asthma. Martin et al.<sup>(13)</sup> found that only 39 of 72 subjects with well-characterized asthma showed a greater than 5% improvement in FEV<sub>1</sub> within 6 weeks of regular ICS use. These authors did not find any biomarker that prospectively could determine which subjects would show improvement and which would not. These same authors had previously shown a highly variable FEV<sub>1</sub> response to ICS.<sup>(14)</sup> Because the change in FEV<sub>1</sub> not a direct action of ICS and almost 40% of subjects with asthma may not show improvement in FEV<sub>1</sub> following treatment with ICS, SAC-RAT members did not believe that FEV<sub>1</sub> alone should be used as the primary outcome for establishing therapeutic equivalence of ICS products.

The Health Canada draft guidance recommends that a three-arm, randomized, placebo-controlled trial be undertaken to establish therapeutic equivalence. The three arms

should include the Canadian Reference product, the SME product, and a placebo. The trial should be powered on an anti-inflammatory outcome used induced sputum eosinophil counts. Although other biomarkers of airway inflammation could be used (e.g., eNO) the committee suggested that induced sputum eosinophil counts were currently the most robust measurement.<sup>(12)</sup> Although eNO in asthma may be useful in assessing airway inflammation, in the subset of steroid-naïve subjects, airway eosinophils may be a more specific marker of ICS responsiveness.<sup>(15)</sup> The committee acknowledged that a crossover design could be considered but the duration of time to allow recovery of eosinophil counts back to baseline after exposure to ICS should exceed greater than a 2-week washout period between tests.<sup>(16)</sup> In contrast, a parallel trial design would allow study duration to be as short as 3 weeks in total.

To test for therapeutic equivalence, the dose of ICS chosen should be on the steep slope of the ICS–eosinophil dose–response curve. In general, the greatest absolute reduction of sputum eosinophil counts occurs at ICS low doses.<sup>(14)</sup> The greatest effect on sputum eosinophils in eosinophilic bronchitis occurred at a dose of 50 µg of inhaled fluticasone and plateaued at 200 µg.<sup>(17)</sup> Therefore, the lowest single dose of Canadian Reference product ICS should be used for a therapeutic equivalence trial.

The population to be tested should have mild asthma and be clinically stable. The committee recommended that subjects be steroid naïve (defined as no use of ICS for at least 6 weeks). Not all subjects with asthma have evidence of eosinophilic airway inflammation,<sup>(18)</sup> and these subjects to tend to be steroid unresponsive. Therefore, subjects should be chosen with at least 3% of induced sputum cell counts consisting of eosinophils. In this manner an ICS responsive population could be prospectively defined.

Coprimary endpoints for the therapeutic equivalence trial should be an inflammatory outcome (e.g., sputum eosinophil counts or eNO) as well as change in prebronchodilator FEV<sub>1</sub>. Then clinical efficacy could be defined as a reduction of at least a 50% in eosinophils compared with Placebo. This would ensure that both the SME product and Canadian Reference product are biologically active in the chosen subjects. In addition, mean FEV<sub>1</sub> of SME and Canadian Reference products should show an improvement of at least 10% compared with placebo. Therapeutic equivalence followed a standard definition: the 90% confidence interval of the relative mean FEV<sub>1</sub> (based on the log-transformed data) of the SME to the Canadian Reference product should be within 80–125%. Similarly, the 90% confidence interval of the relative mean eosinophil count (based on the log-transformed data) of the SME to the Canadian Reference product should be within 80–125%. Safety should be evaluated with a pharmacokinetic (PK) study evaluating the systemic exposure following administration of the SME relative to the Canadian Reference product. This could be used as a surrogate marker for possible long-term systemic effects. A single-dose study at the upper limit of the dosing range should be used. If blood or plasma levels are too low for reliable analytical measurement then a pharmacodynamic (PD) study using changes in the hypothalamic–pituitary–adrenal axis (HPA) should be undertaken.

The trial design outlined above would clearly establish whether therapeutic equivalence and safety exists. It would

meet the committee recommendations that subjects receiving placebo therapy be exposed for shortest duration possible and be unlikely to experience significant exacerbations. This type of trial with steroid naïve asthmatic subjects has been successfully completed by a Canadian multicenter trial organized by AllerGen NCE, a Canadian consortium of asthma and allergy investigators.<sup>(19)</sup> It is both feasible and doable in a safe and expedient manner. General COPD Trial Considerations for FDDC Products

SAC-RAT considered two specific COPD products. The first was FDDC, and the second was LABAs. There is not a published guidance but SAC-RAT deliberations are available on-line ([http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/sci-com/resp\\_allerg/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/sci-com/resp_allerg/index-eng.php)). At the time of these deliberations the only FDDC products on the Canadian market were ICS+LABA combinations.

The committee believed that FDDC products should be reserved for more severe patients, consistent with Canadian Thoracic Society Guidelines<sup>(20)</sup> recommendations that ICS be added after optimal long-acting bronchodilator therapy. Using FDDC products may increase the risk of adverse events (e.g., increased risk of pneumonia and infectious bronchitis associated with the use of ICS<sup>(21)</sup>) over the use of long-acting bronchodilators alone.

The committee agreed that each component of the FDDC should have a discernable role but that there need not be an independent test for each monocomponent. This would be particularly true for ICS because there is not an indication for monotherapy with ICS in COPD. As well, the role of a true placebo group (i.e., no active COPD therapy) was considered to be unethical if a prolonged trial were undertaken. There are now multiple trials showing significant long-term benefits of long-acting bronchodilators in COPD.<sup>(21–23)</sup> Therefore, participants in any trial should receive an active standard of care as a comparator.

Any trial for FDDC products should be a randomized controlled, three-limb, parallel limb. It should last a minimum of a 1 year with FEV<sub>1</sub> as a coprimary outcome. Other outcomes could include COPD specific quality-of-life questionnaires to claim reduction of COPD symptoms; 6-min walk test to claim improvement of exercise capacity; well-defined moderate-to-severe COPD exacerbations to claim reduction of COPD exacerbations. The committee believed that, at the time of publication of its proceedings, there were not any reliable biomarkers that could be used as meaningful outcomes in COPD.<sup>(24)</sup> Therefore, the committee recommended that the use of any biomarker would have to be negotiated with Health Canada as new evidence becomes available. These recommendations were aimed primarily for a new drug submission for FDDC products in COPD.

### LABA SME Trial Considerations

The committee proceedings were less detail regarding LABA SME products. SAC-RAT members were concerned that stand-alone LABA medications could be misused as asthma monotherapy despite the well-recognized increased mortality associated with this practice.<sup>(25)</sup> The concern centered on the possibility that asthma patients could be misdiagnosed as COPD and then treated inappropriately. Unfortunately, COPD patients are, in fact, often misdiagnosed based upon the practice of using only a clinical

impression without spirometric confirmation. This diagnostic approach is common and is inherently unreliable.<sup>(26)</sup> However, because there are clear indications for LABA therapy in COPD the committee members believed that stand-alone LABA SME products should be allowed to be brought onto the Canadian market.

SAC-RAT members suggested that any trial for therapeutic equivalence of a LABA SME product should be performed in a population that is stable and have spirometric confirmation of GOLD stage 2 and/or 3 COPD. The population should be representative of the general Canadian COPD population with both male and female subjects included and subjects should be age 40 years or greater. They should have a smoking history of at least 10 pack-years. There was a lack of committee consensus regarding whether subjects demonstrating partial reversibility of airflow obstruction should be included. The design should include a three-arm, parallel, double-blind, double-dummy trial comparing SME product, Canadian Reference product, and placebo. The lowest dose of LABA of Canadian Reference product should be tested. As a primary efficacy endpoint, the area under the curve (AUC) of the FEV<sub>1</sub> was recommended. To show equivalence, both the area under the curve and the shape of the curve (as assessed by the peak and trough) over a 12-h period should be significantly different from placebo but similar for the SME product and Reference product. Secondary endpoints were not recommended. The primary safety trial should be a PK study using a single-dose crossover at the upper limit of the dosing range.

Secondary safety signals would include comparison of: QTc, serum potassium, vital signs, and blood glucose. The committee did not believe that a 1-year safety study was needed for SME LABA products indicated for COPD. Once the SME LABA product showed bioequivalence to the Canadian Reference product then Health Canada's usual standards should apply. If, for any reason, the SME product was submitted to Health Canada as a New Drug Submission then a 1-year study would be required.

## Summary

The SAC-RAT provided detailed recommendations to Health Canada regarding design of a therapeutic equivalence trial to compare a subsequent market entry ICS product with a Canadian Reference product. The committee recommended that any trial use a marker of airway inflammation, preferably induced sputum eosinophil counts, as a coprimary outcome with FEV<sub>1</sub>. The committee also discussed trials regarding fixed-dose drug combinations or long-acting  $\beta$ -agonists for COPD. These deliberations are available at the Health Canada Website but they as yet not fully developed.

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## Author Disclosure Statement

The author declares that no conflicting financial interests exist.

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