# Asthma

Prohibited Substances: Beta-2-agonists, glucocorticoids

## 1. Introduction

Asthma is a syndrome of the respiratory airways manifested by recurrent episodic symptoms. It is associated with variable airway obstruction that is reversible either spontaneously or with treatment, and the presence of airway hyper-responsiveness and chronic airway inflammation.

There is a high prevalence of these features in active competitive athletes, often in the form of exercise-induced asthma (EIA) or exercise-induced bronchoconstriction (EIB). Exercise induced asthma (EIA) may be defined as a transient airway narrowing induced by exercise in an individual with asthma, while exercise induced bronchoconstriction (EIB) represents the reduction in lung function occurring after exercise.

Asthma is not a uniform disease, and it is acknowledged that the diagnosis of asthma can pose difficulties. The prevalence of respiratory symptoms is high in athletes in general and the diagnosis of asthma cannot be made based on subjective symptoms only.

It is therefore recommended that all athletes who may be prescribed asthma medications seek a clear diagnosis from a respiratory specialist and undergo the appropriate tests to optimize management and to exclude other possible diagnoses. This is mandatory if a TUE is being sought to prescribe a systemic glucocorticoid (GC) in competition or a prohibited inhaled beta-2 agonist in- and out-of-competition.

## 2. Diagnosis

### a. Medical history

The medical history should include a detailed history of symptom presentation and aggravating factors, acute exacerbations and emergency department attendance and the need for courses of systemic GC.

Symptoms suggestive of asthma include episodic or recurrent wheezing, shortness of breath, coughing or breathlessness provoked by hyperventilation, exercise or other stimuli, and/ or persistent cough following a respiratory tract infection, frequent “colds” without fever, or specific seasonal influences and intermittent nocturnal symptoms. In sport, examples of potential aggravating factors include variations in ambient temperature, endurance training especially when exposed to cold air or pollution such as from combustion engines or swimming pool chemicals.

There may also be a history of childhood respiratory problems, rhinitis, allergic conjunctivitis or dermatitis and a family history of asthma, atopy and allergies. In these cases, the development of asthma may be part of an atopic predisposition.

Other factors important to the medical history are the age of onset of asthma and past history of prescribed medication, including the detailed use of inhaled beta-2 agonists and inhaled GCs, as well as acute asthma exacerbations, including hospital admissions or emergency department attendance and previous treatment with oral GC.

Additional helpful information would include a diary of symptoms and peak flow recordings and results of previous investigations, such as relevant skin prick tests, total IgE, specific IgE to seasonal and perennial allergens, FeNO, total eosinophil count in peripheral blood, spirometry reports and any previous bronchial provocation tests at any age.

The presence of co-morbidities or conditions that mimic asthma, such as hyperventilation syndrome, inducible laryngeal obstruction, non-reversible obstructive pulmonary disease, dysfunctional breathing, cardiac valvular disease, myocardial ischemia, heart failure, pulmonary vascular diseases, gastroesophageal reflux or psychological problems, should be considered.

## b. Diagnostic criteria

The diagnosis of asthma demands the synthesis of the medical history with physical examination and appropriate laboratory or field tests. In athletes, recurrent symptoms of airway obstruction such as chest tightness, wheeze and cough provoked by hyperventilation, exercise or other stimuli, are a diagnostic prerequisite for asthma or EIA. In addition, there should be objective evidence of the reversibility of airflow obstruction or airway hyper responsiveness on bronchial provocation testing. Laboratory tests alone are not sufficient for the diagnosis, and the diagnosis cannot be made without objective measurements of variable airway obstruction.

In the case of an asthma diagnosis in childhood made before puberty, the diagnostic workup must be repeated in adulthood to confirm the diagnosis of asthma.

The involvement of a respiratory physician is prudent and may be required in difficult cases. This is especially important when the diagnosis is uncertain or when there may be other conditions that mimic asthma.

**Physical examination**

Although the physical examination in EIA may be normal in the office it should be performed in order to:

- Verify present or recent upper or lower respiratory tract infections;
- Assess if airflow obstruction is present at rest;
- Identify differential diagnoses or co-morbidities.

## Laboratory Testing

### Pulmonary function

Spirometry is a more sensitive measure of airflow than peak expiratory flow (PEF) and consequently is the best reference method and the most objective indicator of asthma severity. PEF measures are nevertheless useful, particularly for the patient, to follow treatment responses. A carefully kept peak flow diary should be established to allow the clinician to chart the patient over time.

Spirometry in an asthmatic patient will demonstrate a typical pattern of obstructive airway disease (reduced FEV1/FVC ratio) with a diminished expiratory flow. Specific cut-off points for spirometry are recommended in the accompanying references. However, many elite athletes have levels of lung function above normal predicted values and therefore normal lung function may still represent a sign of airway obstruction, and a reversibility test is recommended. An increase of at least 12% and 200 ml in FEV1 following the use of an inhaled beta-2 agonist is the standard diagnostic test for the reversibility of airway obstruction.

If the patient history suggests asthma, but the spirometry is normal and/or the reversibility test is negative, a bronchial provocation test is recommended.

### Airway responsiveness

A bronchial provocation test can be performed with physiological (exercise, eucapnic voluntary hyperventilation) or pharmacological (methacholine, mannitol, hypertonic saline, histamine) stimuli. The test evaluates the airway responsiveness in patients with asthma or atypical chest symptoms of indeterminate etiology. To accurately evaluate these tests, the patient should not be using bronchodilator or anti-inflammatory therapy prior to the provocation test or the medication should be discontinued for the testing. For short acting beta-2 agonists this will be for 8 hours, inhaled GC and leukotriene receptor antagonists, 24 hours, and for long-acting beta-2 agonists, 48 hours, prior to testing. A test-specific significant decrease in $FEV_1$ following the administration of a provocative stimulus other than exercise is considered to be diagnostic of airway hyper responsiveness and comparable to the stimulus of exercise.

These tests may provoke significant respiratory symptoms and should only be undertaken in a supervised setting with appropriate medical support, e.g., in an established respiratory laboratory, and preferably in collaboration with a respiratory physician.

It is not within the scope of this document to provide the full details of each bronchial provocation test. Further reference should be made to the European Respiratory Society (ERS) and American Thoracic Society (ATS) standards as well as IOC Asthma Consensus Document6.

Common provocation tests, in no specific order, include the following:

- Exercise Challenge Tests (field or laboratory) (≥10% fall of $FEV_1$ over 2 consecutive time points);
- The Eucapnic Voluntary Hyperpnea (EVH) test (≥10% fall of FEV1 over 2 consecutive time points);

- Methacholine Aerosol Challenge (≥20% fall of FEV1 - PC20<4mg/mL, [steroid naïve]) or if taking inhaled GC > 1 month, then PD20 should be less or equal to 1600 micrograms or PC20 less or equal to 16.0 mg/mL;
- Mannitol Inhalation (≥ 15% fall in FEV1 after challenge);
- Hypertonic Saline Aerosol challenge (≥15% fall of FEV1);
- Histamine Challenge (≥ 20% fall of FEV1 at a histamine concentration of 8mg/mL or less during a graded test of 2 minutes).

A positive response to any one of the above provocation tests confirms airway hyper responsiveness (if not already confirmed by spirometry and bronchodilatation test). Sometimes the athlete may have positive response to one test and negative response to another. Also, some athletes may be free of symptoms and have a negative provocation test response during periods of rest, while a test can be positive during intense periods of competition.

### c. Summary

In accordance with the International Standard for TUEs and consistent with current best medical practice, the medical file required to support an application for a TUE in the case of an athlete with asthma or any of its clinical variants must include the following details:

- a complete medical history as described and clinical examination with specific focus on the respiratory system;
- a spirometry report with flow volume curve;
- if airway obstruction is present, the spirometry will be repeated after inhalation of a short acting beta-2 agonist to demonstrate the reversibility of bronchoconstriction;
- in the absence of reversible airway obstruction, a bronchial provocation test is required to establish the presence of airway hyper responsiveness;
- exact name, speciality and contact details of examining physician;
- if the athlete reapplies for a TUE that has expired, the application should include the documents that confirm the initial diagnosis as well as the reports and pulmonary function tests from regular asthma follow-up visit.

## 3. Treatment

The treatment of EIA and of asthma in athletes should follow the same international guidelines as for the individual with general asthmatic symptoms. Inhaled GC used on a regular and ongoing basis is the mainstay of treatment for asthma and the use of inhaled beta-2 agonists should be restricted to emergency or breakthrough symptoms and pre-exercise. Leukotriene receptor antagonists and anticholinergic agents can be used as described in the GINA guidelines.

Allergies and rhinitis should be treated appropriately and non-pharmacological measures, such as avoidance of allergens, pollutants and exercise in extreme cold, are of crucial importance. Strenuous exercise during an acute exacerbation of asthma is not advisable.

Asthma may be a life-long condition. In the case of EIA, the duration of treatment will be symptom dependent. The effect of any treatment modification should be monitored and the treatment adjusted thereafter. A childhood asthma diagnosis and the need of medication must be re-evaluated after puberty.

In sports, only certain inhaled beta-2 agonists are permitted and only when used by inhalation at therapeutic dosages. The athlete should always be treated at the lowest medication level necessary to control symptoms. A prescription for a beta-2 agonist that simply states “as needed” is rarely appropriate and should be clarified by the prescribing physician with dosage and frequency described. Nevertheless, the athlete’s health should never be jeopardized by restricting medication when necessary (see 9. Special Circumstances). It should however be emphasized that the overuse or prolonged use of short- and long- acting beta-2 agonists can lead to tolerance and may have detrimental effects to health.

It is important that a correct inhaler technique is learned and monitored. Use of a spacer, (also known as aerosol-holding chambers, add-on devices and spacing devices), may make it easier to inhale the medicine delivered by a pressurized MDI, improve the lung deposition and decrease the deposition in the mouth and throat.

Although nebulizers are by definition inhalation devices and thus not prohibited as a method, the inhalation of salbutamol in doses recommended by the manufacturer is most likely to result in urinary levels of salbutamol exceeding the urinary threshold of 1,000 ng/ml. Thus, the use of salbutamol with a nebulizer requires a TUE. However, a TUE for nebulized salbutamol would be granted only in rare situations, such as a severe acute asthma attack treated in an emergency room setting. In otherwise healthy adults, the use of metered dose inhalers with a spacer has been demonstrated as effective as the nebulized drug in managing acute exacerbations of asthma.

All athletes should have a written action plan for an exacerbation and receive appropriate education on their disease, its assessment and treatment.

If an athlete has an exacerbation of their asthma, it is recommended that they seek immediate assessment and treatment from a physician. However, in exceptional situations this may not be possible, and the athlete must initiate emergency or urgent treatment and follow an action plan such as repeated beta-2-agonist inhalations and/or per oral glucocorticoid. In these situations, the event should be documented, ideally with objective signs which could be helpful for the assessment of a possible retroactive TUE application. Moreover, the athlete should contact their treating physician, as soon as possible, for a review of the acute event and evaluate and considering revising future action plans.

## a. Name of prohibited substances

**Beta-2 agonists**

As per the Prohibited List: All selective and non-selective beta-2-agonists, including all optical isomers, are prohibited at all times, including but not limited to: arformoterol, fenoterol, formoterol, higenamine, indacaterol, levosalbutamol, olodaterol, procaterol, reproterol, salbutamol, salmeterol, terbutaline, tretoquinol (trimetoquinol), tulobuterol, vilanterol. Therefore, use of these substances require a TUE. However, there are exceptions, as described below:

### i) Salbutamol

Inhaled salbutamol is not prohibited when taken up to maximum doses of 1,600 micrograms over 24 hours; in divided doses not to exceed 600 micrograms over 8 hours. However, the presence of salbutamol in the urine in excess of 1000 ng/mL is presumed not to be a therapeutic use of the substance and will be considered as an adverse analytical finding. The athlete would then need to document the details of his/her medical condition and medication use. The athlete may then be required to prove, by a controlled pharmacokinetic study (see **Annex 2**) that the abnormal test result was the consequence of the use of a therapeutic dose (maximum 1600 micrograms over 24 hours in divided doses not to exceed 600 micrograms over 8 hours starting from any dose) of inhaled salbutamol.

If a dosage in excess of 1600 micrograms in 24 hours or 600 micrograms in 8 hours, is legitimately required by the athlete, then a TUE must be requested. In case of an emergency or an exacerbation, a retroactive TUE application should be submitted as soon as possible to the appropriate anti-doping organization. Note that salbutamol, as a short-acting B-2 agonist, is often used as a rescue medication.

The use of salbutamol with a nebulizer would likely lead to urinary levels exceeding the urinary threshold of 1,000 ng/ml and would require a TUE.

### ii) Salmeterol

Inhaled salmeterol when taken up to a maximum dose of 200 micrograms over 24 hours is not prohibited. For doses exceeding 200 micrograms over 24 hours a TUE must be requested. The manufacturer does not however recommend use of salmeterol in doses exceeding 200 micrograms over 24 hours, and it is not likely that a TUE will be granted for dosages exceeding the manufacturer's recommendations.

### iii) Formoterol

Inhaled formoterol when taken up to a maximum delivered dose of 54 micrograms over 24 hours, is not prohibited. The presence in urine of formoterol in excess of 40 ng/mL is presumed not to be a therapeutic use of the substance and will be considered as an Adverse Analytical Finding unless the Athlete proves, through a controlled pharmacokinetic study, that the abnormal result was the consequence of the use of no greater than 54 micrograms delivered over 24 hours. If a dosage in excess of 54 micrograms over 24 hours is required by the athlete, then a TUE must be requested.

In the WADA Prohibited List, formoterol is expressed in terms of the delivered dose (see **Annex 1** of this document).

The expression of the dose on the label of a formoterol delivery device can vary between countries; the label may state the dose in terms of the amount that enters the inhalation device (metered dose) or the amount leaving the mouthpiece (delivered dose). This will be explained on the patient information leaflet for the product.

### iv) Vilanterol

Inhaled vilanterol, when taken up to the manufacturer's maximum recommended (metered) dose of 25 micrograms over 24 hours is not prohibited. For doses exceeding 25 micrograms over 24 hours a TUE must be requested.

**Comments on the prescribing and granting of prohibited inhaled beta-2 agonists**

A TUE can be granted for a prohibited beta-2 agonist in recommended therapeutic doses if asthma is clearly diagnosed (preferably by a specialist in respiratory medicine) and the application includes verification by standardised respiratory function tests as described in Section 2 of this document.

Since there are beta-2 agonists that are permitted by inhalation in therapeutic doses up to certain threshold doses, the physician must explain why the prescribed alternate beta-2 agonist was the most appropriate, e.g. based on experience, side-effect profiles or other medical justifications, including where applicable, geographically specific medical practice, and the ability to access the medication. Further, it is not always necessary to try and fail alternatives. The intention not to deny the use of the preferred beta-2 agonist, particularly where a treatment regimen has already been established.

Please note that all beta-2 agonists are prohibited but some are permitted by inhalation at therapeutic dosages as described in the List (salmeterol, salbutamol, formoterol and vilanterol). This is not a reflection of their relative ergogenic potential but takes into consideration factors such as the potential routes of administration and laboratory technical reasons.

## Systemic glucocorticoids

As of the 2022 Prohibited List, oral, rectal or any injectable routes of administration of glucocorticoids (GCs) are prohibited in-competition only. However, an in-competition urine sample may show GC levels above the established laboratory reporting levels even though administration occurred out-of-competition. In accordance with the Code, a resulting positive doping test, known as an adverse analytical finding (AAF), could render the athlete liable to a sanction under the concept of Strict Liability. However, as per ISTUE Article 4.1e, the athlete is permitted to apply retroactively for a TUE if there is an in-competition AAF from out-of-competition use.

In certain situations, athletes with well documented medical conditions such as asthma may require intermittent or recurrent courses of oral glucocorticoids and could be granted TUEs for up to 12 months. However, it is anticipated that evidence of deterioration of asthma (such as Peak Flow or Spirometry tests) will be obtained and recorded before commencing a new course of GCs.

In such cases, conditions should be attached to the TUE approval certificate, requesting either:

1. A notification in writing to the TUEC at the time, or soon after, the GCs are used throughout the 12-month period, or;
2. A written summary of use, from the treating doctor, at the end of the 12-month period.

Note: the TUEC reserves the right to request relevant medical records during the time of approval.

These documents are to ensure that systemic GCs are not used around the time of competition without good medical reason and will then be used by the TUEC to determine if subsequent approvals for long term use of GCs will be approved in future. It is recommended that a more cautious approach should be used with athletes from sports with a higher risk of GC abuse, as longer-term approvals may not be appropriate for these groups.

### b. Non-prohibited alternative treatments

- Leukotriene receptor antagonists
- Anticholinergics
- Cromones
- Theophyllines (Xanthines)
- Anti-lgE agents
- Anti-IL5

## 4. Consequences to health if treatment is withheld

- Chronic ill health
- Acute exacerbations of asthma
- Sudden death from “status asthmaticus”
- Inability to participate fully in physical activity and competitive sport

## 5. Treatment monitoring

Ongoing monitoring should involve assessment of asthma control criteria as described in GINA or equivalent national asthma management guidelines (including exacerbations, use of acute emergency services and the need for courses of systemic glucocorticoid therapy). The effect of treatment and the influence of exercise can also be assessed, either through a bronchoprovocation test or post exercise monitoring of expiratory flows. Inhaler technique and adherence to treatment should be monitored at each visit. The treatment should be adjusted according to control criteria as described in GINA[7], including objective measures and exercise tolerance.

An exacerbation of asthma requiring treatment with prohibited substances should be objectively documented, for example by spirometry and peak expiratory flow recordings. In acute emergency situations, the athlete’s health is the first priority, but the effect of the treatment and the follow-up after an emergency situation should be well documented.

When the treatment is modified, the effect of the treatment should be objectively monitored and recorded to verify a beneficial effect of the new treatment. The treatment should be modified or stopped if the diagnosis is revised.

# 6. TUE duration and recommended review process

A TUE can be granted for a prohibited beta-2 agonist if the asthma diagnosis is adequately established and an explanation for the prescription of a prohibited beta-2 agonist is included in the application. An acute exacerbation requiring treatment with prohibited substances or doses exceeding the allowed daily maximum should be documented as objectively as possible.

The recommended duration of the TUE for an asthmatic athlete is 4 years with an annual review by a physician experienced in treating athletes. The first TUE for a medication may be of shorter duration, for example 1 year, and documentation of positive effects of the chosen treatment should be provided when applying for a TUE after the initial treatment period.

Asthma is a lifelong condition. For renewal of a TUE, new diagnostic workup off-medication should not be required, if the initial diagnosis has been adequately made and verified after puberty. A stable asthmatic patient should not stop medication without consulting his/her physician, since this may have detrimental health effects.

In some cases, an Anti-Doping Organization may impose conditions such as a review by a specialist within a certain time frame.

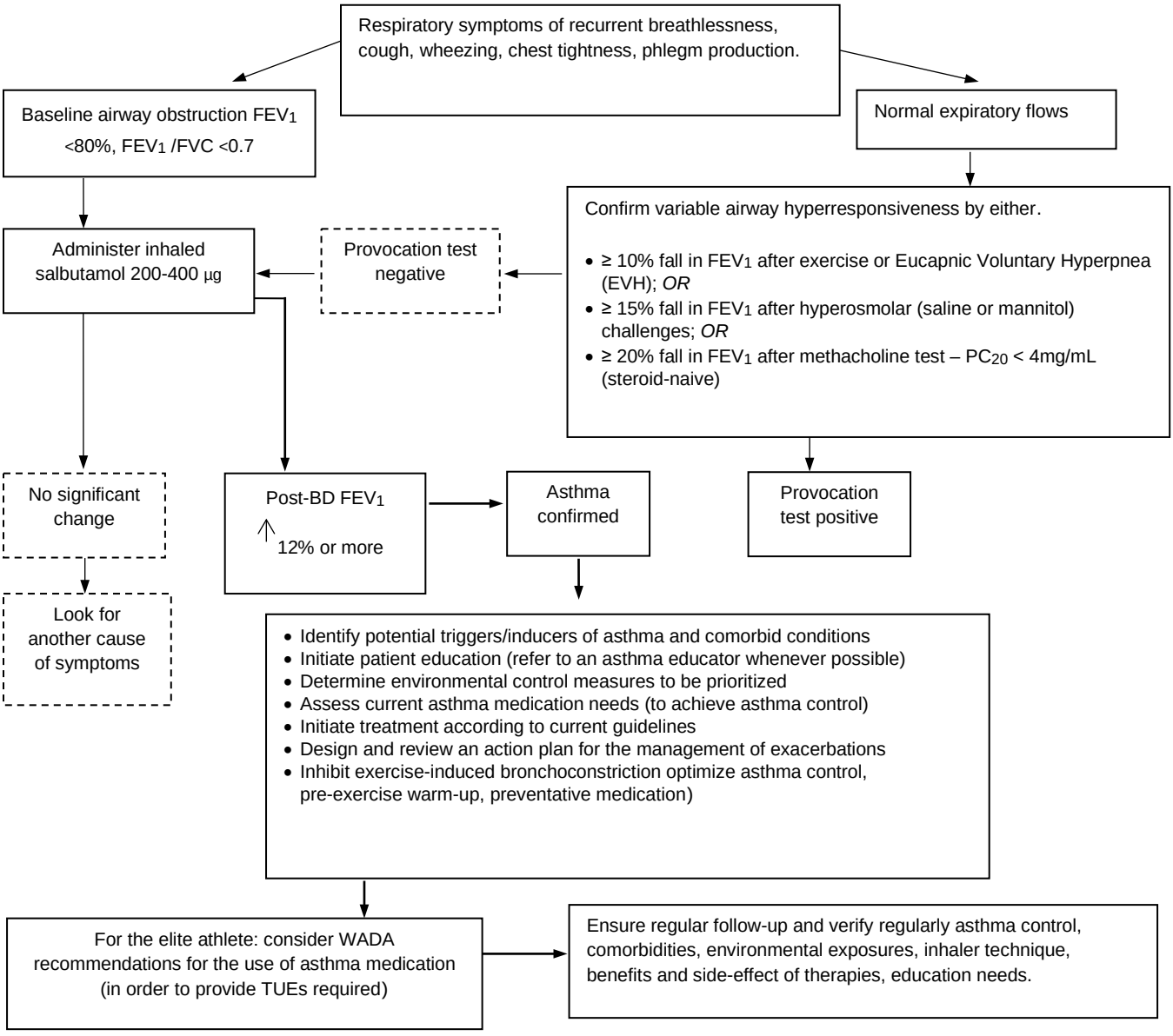
# 7. Any appropriate cautionary matters

The athlete should not be exposed to any tests of bronchial provocation at the time of, or immediately (6 weeks) prior to a major sporting event when their health may be significantly affected. The athlete should plan accordingly. The necessity for tests and options available would have to be evaluated on a case-by-case basis.

**An athlete's health should never be jeopardized by withholding medication in an emergency**

# Asthma management for the athlete

BD: Bronchodilator; FVC: forced vital capacity




Source: p. 257, Fitch K et al. Asthma and the elite athlete: Summary of the IOC Consensus Conference Lausanne, Switzerland, January 22-24, 2008. J Allergy Clin Immunol 2008 Aug; 122(2):254-60.

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# Annex 1

## Formoterol

**There are number of different inhalation devices available using formoterol. The dose may be expressed as the amount that enters the inhalation device (metered dose) or the amount leaving the mouthpiece (delivered dose) depending on each country's labelling standards. For the purposes of this document, formoterol is expressed in terms of the delivered dose which is the amount that leaves the mouthpiece of the inhalation device and is available for inhalation.**

From 2013, inhaled formoterol to a maximum delivered dose of 54 micrograms (mcg) in 24 hours is permitted in sport. When inhaled formoterol as the fumarate salt, either singly or in combination with budesonide (commonly marketed worldwide as Symbicort) is delivered as a powder by a turbuhaler, 75% of the administered dose is released and thus delivered. Hence, a preparation containing 12mcg of formoterol delivers to the patient ~9mcg per inhalation. If two inhalations twice a day (i.e. 48mcg) are administered, the delivered dose to the patient is 36mcg.

**The WADA Prohibited List refers to the inhaled (delivered) dose and not the dose released from the inhalation device.**

The standard dose of formoterol is 24 mcg/day with a maximum of 36 mcg/day. In some countries, the maximum dosage may be 54 or even 72 mcg/day, however this is usually only for short term treatment of asthma during exacerbations. In the rare case in which a dosage of greater than 54 mcg (inhaled) over 24 hours is prescribed, the athlete will be required to apply for a Therapeutic Use Exemption with appropriate pulmonary function tests and an explanation from a respiratory specialist. If this is due to an acute emergency asthma exacerbation, then an emergency/retroactive TUE should be submitted at the earliest convenience as per the International Standard on TUE.

Unless a TUE was granted, the presence in urine of formoterol in excess of 40 ng/mL is presumed not to be a therapeutic use of the substance and will be considered as an Adverse Analytical Finding unless the Athlete proves, through a controlled pharmacokinetic study, that the abnormal result was the consequence of the use of inhaled formoterol at no greater than 54 mcg over 24 hours.

# Annex 2

## Key guiding principles for a controlled excretion study

Key guiding principles for a controlled pharmacokinetic study as referred to in the Prohibited List:

1. The study shall be conducted in a controlled setting allowing a strict and independent supervision of the drug administration (route, dose, frequency, etc.) and sample collection (matrix, volume, frequency) protocol.

2. A wash-out period should be established in order to collect baseline urine or blood samples just prior to the administration of the drug, i.e., the athlete should not be taking the medication before the test. Necessity of the drug for health reasons as well as the known pharmacokinetics of the product will need to be taken into account, if necessary.

3. Collection of urine samples shall occur whenever that athlete wishes to deliver samples but no less than every two hours during the monitoring period. Sampling periods should be adjusted to the known pharmacokinetic of the product (e.g., every 30 min. or night collections might be considered, if justified).

4. The athlete shall take the drug in accordance with the treatment course (dose, frequency, route of administration) declared in the doping control form or, alternatively, following the therapeutic regime indicated on a granted TUE, if any. The administered dose shall never exceed the maximal dose/frequency recommended by the drug manufacturer or a safe level prescribed by the athlete's physician.

5. The samples shall be analyzed in a WADA accredited laboratory with the validated relevant anti-doping method. Correction for specific gravity shall be applied in accordance with the provisions of the International Standard for Laboratories and related Technical Documents.

6. The WADA accredited laboratory will issue a comprehensive report indicating the results of the analyses and interpretation, if needed. If deemed necessary, review of the results by an independent expert can be sought by the Testing Authority.