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**COMMITTEE ON HERBAL MEDICINAL PRODUCTS
(HMPC)**

DRAFT

REFLECTION PAPER ON THE ADAPTOGENIC CONCEPT

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Comments should be provided using this [template](#) to hmpc.secretariat@emea.europa.eu
Fax: +44 20 75 23 70 51

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1. Introduction

The term “adaptogen” is attributed to different herbal medicinal products, among them preparations deriving from *Eleutherococcus senticosus* (*Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim.). Other examples for herbal adaptogens may include preparations from *Panax ginseng* C. A. Meyer, *Schisandra chinensis* (Turcz.) Baill. and *Rhodiola rosea* L.. During the drafting of the ‘Community herbal monograph on *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim., radix’ (EMA/HMPC/244569/2006), the HMPC considered how to approach the assessment of adaptogenic herbal medicinal products in general. Although the HMPC discussed the example of *Eleutherococcus* only, similar considerations may be necessary with other herbal substances with adaptogenic properties.

2. Scope

The intention of this reflection paper is to clarify the term ‘adaptogen’ and to reflect the current thinking of the HMPC on the interpretation of the term ‘adaptogen’.

3. Clarification of the term “adaptogen”

Adaptogenic substances are stated to have the capacity to normalize body functions and strengthen systems compromised by stress. They are reported to have a protective effect on health against a wide variety of environmental assaults and emotional conditions.

The term ‘adaptogen’ was originally established by N. V. Lazarev (1947). The general pharmacodynamic characteristics of an adaptogenic substance were defined by Brekhman and Dardymov (1969) as follows:

- a) an adaptogen is almost non-toxic to the recipient;
- b) an adaptogen tends to be non-specific in its pharmacological properties and acts by increasing the resistance of the organism to a broad spectrum of adverse biological, chemical, and physical factors;
- c) an adaptogen tends to be a regulator having a normalizing effect on the various organ systems of the recipient organism.

The term ‘adaptogen’ has recently been used as a functional term by some health authorities (Panossian et al, 1999, from FDA, 1998; Panossian, 2003; Panossian, Wagner, 2005).

In order to avoid confusion, it is necessary to differentiate the term ‘adaptogen’ from traditional herbal medicinal products of related action:

Tonics are substances, which mitigate conditions of weakness or lack of tone within the entire organism, or in particular organs (Bundesgesundheitsamt 1988; Aschner 1953). The term is typical for traditional medicine, where tonics are used in conditions of “asthenia¹”.

Stimulants cause a temporary increase in work-capacity, which is followed by a period of decreased work-capacity. The term is used in modern and in traditional medicine.

In contrast to stimulants, adaptogens are reputed to cause an increased work-capacity that is not followed by a decrease.

¹ The term "Asthenia" used in traditional medicine describes a health status / personal disposition of weakness and loss of strength / energy that may be related to the person in general or to individual organs. The symptoms covered by the term differ from modern classifications such as ICD 10 R 53: "Malaise / fatigue, Asthenia NOS" and F 48.0 "Neurasthenia". Some symptoms associated with the traditional term might be classified under ICD 10 F 45.3 "somatoform disorders".

More recently, plant adaptogens have been defined as compounds that increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors (Panossian et al., 2005).

4. Pharmacological studies in connection with the term adaptogen

The earliest studies of adaptogens investigated primarily their ability to increase the mental and physical working capacity in humans (Medvedev, 1963; Dalinger, 1966a). After those studies characteristic differences between the effects of adaptogens and those of CNS stimulants became evident (Fulder, 1980, in Panossian & Wagner, 2005).

Stimulants that increase the activity of the sympathetic nervous system, may produce a sense of euphoria and may be used to increase alertness and the ability to concentrate on mental tasks.

Plant adaptogens are reported to stimulate the nervous system by mechanisms that are claimed to be different from those of stimulants, being associated rather by metabolic regulation of various elements of the stress-system and modulation of stimulus-response coupling (Wagner et al., 1994; Panossian et al., 1999; Panossian, 2003).

Adaptogens are reputed to have an anti-stress effect mainly towards stresses of a non-infectious agent. In this aspect adaptogens differ from eg. immunostimulants.

The general purpose of adaptogens is the reduction of stress reactions in the alarm phase, thereby avoiding the exhaustion stage and providing a certain protection against stress. In a similar way, Brekhman (1980) describes the adaptogenic effect as a strengthening of the physiological adaptation.

In addition to their various properties, adaptogens are thought to rebuild strength of the body after stress or fatigue (Baranov, 1982). Clinical trials on adaptogens reported an effective application to persons exposed to high physical and nervous loading, i.e., for athletes. It is reported that muscular activity and nervous loading causes the reaction of stress or stress-reaction that is reduced by usage of adaptogens (Nörr, 1993; Wagner et al, 1994; Wagner, 1995).

5. Pharmacodynamic action and clinical data

5.1 *The role of adaptogens in Phytotherapy*

It is difficult to relate the definition of an adaptogen with the concepts in contemporary pharmacology. The concept of “one drug – one symptom” or “one drug for one disease” is not applicable to adaptogens.

Most modern active substances are directed to well-defined clinical conditions. If preventive actions are intended, they are specific to a certain disease factor, e.g. vaccines, use of anti-virals, or they are directed to a certain pathological factor with a view to reducing the risk of disease, e.g. cholesterol lowering substances.

In contrast to these approaches, the action of adaptogens is reported to be neither directed to eliminate the symptoms of already existing diseases nor is the action specific. If used in an already developed disease, adaptogens are thought to create unspecific effects and in this case they mostly are thought to prevent complications of a disease and to strengthen the general state of the organism.

5.2 *Pre-clinical and clinical data*

A series of experiments, designed to demonstrate this difference between adaptogens and CNS-stimulants at a more basic, biochemical level (Brekhman, Dardymov, 1968, from Panossian et al., 1999), have hypothesized that the adaptogenic action depended on the cellular synthesis of nucleic acids, the effect which would be in sharp contrast to CNS-stimulants. A number of additional studies

were designed to reveal an eventual direct effect on protein/nucleic acid production. These investigations can be divided into two groups: a) in stress situations, and b) under normal conditions. In conclusion it has to be mentioned that the molecular targets of adaptogens which are responsible for activation of DNA and protein synthesis during adaptation are still unknown (Panossian et al., 1999).

Other studies on the mechanism of adaptogen action investigated on increased formation of glucose-6-phosphate (Dardymov, Khasina, 1972, from Panossian et al., 1999).

The chemistry of the secondary constituents of *Eleutherococcus* and their pharmacological effects may support the hypothesis that the reported beneficial effects of adaptogens derive from their capacity to exert direct protective and/or inhibitory action against free radicals. Compounds from *Eleutherococcus* show various levels of anti-oxidant activity (Davydov M & Krikorian AD (2000)). A large number of studies have revealed potent antioxidant properties of constituents of another herbal substance, *Schisandra lignans* (Wang et al., 1994, from Panossian et al., 1999). However, it is worth emphasizing that a reduction of lipid peroxidation or antioxidant effects cannot be supposed to be the main action of the adaptogens, which is evident from the fact that the known strongly antioxidant substances (tocopherols, etc.) do not exhibit adaptogenic properties (Panossian et al., 1999).

One other mode of action of adaptogens has been associated with the neuroendocrine-immune complex and can be directed on the various targets of the system involved in regulation (activation and inhibition) of stimulus-response coupling, which are responsible for defence and adaptation of organism to stressors.

The HMPC is aware of the fact that numerous pre-clinical and clinical studies have been performed with the view to proving the concept of an adaptogen. However, the clinical data have a number of shortcomings such as deficiencies in the description of inclusion and exclusion criteria, description of the medication, diagnosis, study design, analysis etc. There is a wide range of clinical conditions that have been investigated and in some studies the number of patients was very small. None of the studies would be sufficient to substantiate efficacy of *Eleutherococcus* preparations in a clearly defined clinical condition, although, in total, the data available are sufficient to justify further research into the concept of adaptogens.

6. Conclusion

The principle of an adaptogenic action needs further clarification and studies in the pre-clinical and clinical area. As such, the term is not accepted in commonly used pharmacological and clinical terminology. The HMPC is aware of the fact that numerous pre-clinical and clinical studies have been performed with the view to proving the concept of an adaptogen. However, the clinical data have a number of shortcomings such as deficiencies in the description of inclusion and exclusion criteria, description of the medication, diagnosis, study design, analysis etc. There is a wide range of clinical conditions that have been investigated and in some studies the number of patients was very small. None of the studies would be sufficient to substantiate efficacy of *Eleutherococcus* preparations in a clearly defined clinical condition, although, in total, the data available are sufficient to justify further research into the concept of adaptogens. As the term “adaptogen” is considered not appropriate for a marketing authorisation, more clinical studies and data on the efficacy in a well defined clinical condition would be necessary. The concept of adaptogens is sufficient to be considered in the assessment of traditional herbal medicinal products (e.g. monograph on *Eleutherococcus* root)

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