



European Medicines Agency
Evaluation of Medicines for Human Use

London, 8 May 2008
Doc. Ref. EMEA/HMPC/598048/2007

**OVERVIEW OF COMMENTS ON
'REFLECTION PAPER ON ADAPTOGENIC CONCEPT'
(EMEA/HMPC/598048/2007)**

Table 1: Organisations providing comments on the draft 'Reflection paper on adaptogenic concept' as released for consultation on 5 July 2007 until 15 October 2007

Organisation	
1.	Emanon Pharma AB; Per Gruber, Sweden
2.	Interregional Center "Adaptogens"; V. Makarov, A. Shikov, Russia
3.	Swedish Herbal Institute R&D, A. Panossian, Sweden

Table 2: Discussion of comments

(Comments presented here partially address the assessment of *Eleutherococci radix*, please refer to the relevant monograph and list entry and related documents for additional information)

GENERAL COMMENTS TO DRAFT DOCUMENT	OUTCOME
<p>1. In traditional medicine of different countries a number of plants which stimulate the nervous system, decrease depression, enhance work performance, longevity, resistance to high altitude sickness, treat fatigue and symptoms of asthenia subsequent to intense physical and psychological stress have been used. However, not all of them may be classified as adaptogenes. Adaptogenes increase the ability of the body to adapt, and thus its power of resistance against stress and adverse impacts of a physical, chemical or biological nature. The effect should be general and relate to the whole organism, and not just directed at a specific organ. An adaptogenes should have a restoring and balancing effect in both the short and long-term, and be effective independent of any diseases. Adaptogenes may be able to reduce the release of stress hormones and help the body to cope better with stress and other physiological and psychological strains. Adaptogenes are harmless and have no adverse effects, either in the short or long term.</p> <p>2. According to the official classification of drugs in Russian Federation (Register 2007) adaptogenes are included in special group of medicines “Adaptogenes and common tonics”. This group includes over 25 medicinal preparations which represent raw plant material, extracts, tinctures, complex elixirs, and tablets.</p> <p>Herbs and preparation that are classified as adaptogenes in Russian Federation: <i>Aralia manshurica</i> Rupr. et Maxim., <i>Eleutherococcus senticosus</i> (Rupr. et Maxim.) Maxim., <i>Leuzea - Rhaponticum carthamoides</i> (Willd.) Iljin, <i>Oplonanax elatus</i> (Nakai) Nakai, <i>Panax ginseng</i> C. A. Mey, <i>Rhodiola rosea</i> L., and <i>Schizandra chinensis</i> (Turcz.) Baill.</p> <p>Medicinal preparations from all of above mentioned plants were tested in clinics and approved. They are used in officinal medicine in Russia for many years (some of them hundred years). Main adaptogenes were tested in clinics in 1960-1970. Because they were proposed firstly for support of soldiers of Soviet Union army and sportsman there are only limited published data. Nevertheless efficacy of adaptogenes is proved and confirmed. Clinical effects of adaptogenes was published only in recent years, mainly in Russian press (Barnaulof, 2002; Saratikov & Krasnov, 2004; Zhuravlev & Kolyada, 1996)</p>	<p>The HMPC is aware of the facts that are mentioned in the comment. Many of these aspects are addressed in the assessment report for <i>Eleutherococci radix</i>.</p> <p>The inclusion of herbal preparations with adaptogenic properties in the “traditional use” group doesn’t contradict their inclusion into official Pharmacopoeias. However, HMPC will need more detailed information on the adaptogenic properties of the relevant herbal substances/preparations before inclusion of individual herbal preparations in the “well-established use” group. This specific assessment goes beyond the scope of the reflection paper.</p>

GENERAL COMMENTS TO DRAFT DOCUMENT	OUTCOME
<p>3. It turns out that acceptance of the adaptogenic concept, as a new category of herbal medicinal products, depends on availability of clinical studies supported by documentation containing complete description of all details such as diagnosis, patient inclusion criteria, number of patients, study design, analysis, etc.</p> <p>In other words, acceptance what to call these medications in general – the adaptogen or the stimulant, tonic and modulator of non specific immune system (see clarifications below), depend on quite another matter – evidences of their well established use and use in traditional medicine.</p> <p>In fact, adaptogens are not only stimulants, or only tonics, or only immunomodulators, they have polyvalent actions by definition, different mechanisms, but several common features combined in one term - the adaptogen. Numerous publications performed in various countries, demonstrated their stress-protective, stimulating and tonic (general well being, QOL, see below) effects. Even only experiments on animals are enough in order to accept this scientific term (adaptogen) as a functional one. Actually , term adaptogens is very well accepted by herbalists, medical practitioners, physiologists and others, except of pharmacologists which traditionally accept as a pharmacological category a group of medications which usually have:</p> <ul style="list-style-type: none"> - similar chemical structure, - common mechanism of action, - the same pharmacological effect. <p>Adaptogens by definition have several biological effects at once. Their mechanisms of action are associated with stress system and mediated by several key mediators of stress response such as cortisone, nitric oxide, stress activated protein kinases, molecular chaperons (HSP72 and HSC73, transcription factor DAF-16, and other autocoids. Elucidation of mechanisms of actions of different adaptogens depends on our general knowledge about molecular functioning of stress system/neuroendocrine-immune complex.</p>	<p>The inclusion of herbal preparations with adaptogen properties in the “traditional use” group does not contradict with their polyvalent pharmacological actions. These studies add to the plausibility of the accepted traditional use. However, pharmacological actions are not sufficient to substantiate therapeutic efficacy in a well-defined condition. Adaptogens cannot be accepted as a panacea with hundreds of therapeutic indications.</p> <p>HMPC is aware of the fact that some adaptogenic plants, e.g. Eleutherococcus, have been authorised in some Member States on the provisions of well-established use. However, the adaptogenic concept has not been scientifically accepted in the majority of EU Member States. The HMPC concluded that more detailed studies and further information on the adaptogenic principle is needed before inclusion of the relevant herbal preparations in the “well-established use” group. Such information may be found when assessing other herbal substances having such properties. The reflection paper may be updated if the need will arise from the assessment of these substances.</p>
<p>4. Quite another question is with clinical studies supporting well established use of adaptogens. Since adaptogens are traditionally used, some of them for centuries, in order to improve general well being and increase stamina, it is not necessary to perform clinical trials a on large number of patients (In fact already performed clinical trials on adaptogens enrolled totally several thousand participants), because what is required, that is to show statistically significant difference between placebo and verum medication on any sample size of patients. In this aspect, even few trials are enough in order to be sure that traditionally used medication really has beneficial significant effect and that is not an effect of placebo. Examples of several studies on Eleutherococcus with rating 1B-II A are listed below and in the attached file. Requirements regarding diagnosis are not applicable for studies with healthy volunteers.</p>	<p>HMPC has already addressed the issue of the assessment of old non GLP, or non GCP compliant studies in specific guidance. The studies specific to a given herbal substance will be discussed in the relevant assessment reports, e.g. the AR on Eleutherococci radix. The discussion of specific studies exceeds the scope of the reflection paper.</p>

GENERAL COMMENTS TO DRAFT DOCUMENT	OUTCOME
<p>It should be mentioned, that in the 60's and 70's the GLP concept was not fully introduced and documentation and reporting of the results of clinical trials was not on that level all over the world as it is at this day and age. However that does not mean that the clinical trials carried out in 60's and 70's were not well performed and therefore their results are not acceptable and their efficacy is not well established. This statement probably is equally valid to many other drugs, such as aspirin etc. used as official medicine since long ago.</p>	

SPECIFIC COMMENTS ON TEXT

3. Clarification of the term adaptogen

Paragraph no.	Comment and Rationale	Outcome
1.	<p>The history of the herbal substances known as adaptogens appears to begin with Order No 4654-p of the People's Commissars Council of the Union of Soviet Socialist Republics, dated March 4, 1943 and concerning research work "with the purpose of finding...tonic substances" for both soldiers and persons working in the Russian defense industry during the Second World War (Lebedev, 1967; Panossian, 2003). The term adaptogen was originally coined in 1947 by N. V. Lazarev, a pharmacologist, to describe the unexpected effects of dibazol (2-benzylbenzimidazol). Dibazol was found to increase the resistance of organisms to stress in experimental studies – "the state of non-specific resistance SNIR" (Lazarev, 1947).</p> <p>Brekhman and Dardymov (1969) have proposed specific criteria that need to be fulfilled for a substance to qualify as an adaptogen. Thus, an adaptogen must:</p> <ul style="list-style-type: none"> i) produce a nonspecific response, i.e. increase the power of resistance against multiple (physical, chemical or biological) stressors; ii) have a normalizing influence, irrespective of the direction of change from physiological norms caused by the stressor; iii) be innocuous and not influence normal body functions more than required. 	<p>The HMPC is aware of the facts that are mentioned in the comment. Many of these aspects are addressed in the assessment report for Eleutherococci radix.</p>

Paragraph no.	Comment and Rationale	Outcome
1.	There are several strong points of similarity with the explanation of the mode of action of adaptogens (prolonged SNSR) and the concept of allostasis and its multiplex physiological impact on the body in stress . In fact adaptogens have been characterised as “Remedies of allostatic overload” [Klein, 2004]	Allostasis is a relatively new concept of ‘viability through change’ and was first introduced by Sterling and Eyer in 1988 to describe an additional process of reestablishing homeostasis. HMPC considered that the present scientific information is not sufficient to establish a firm link to the issue of adaptogens that is covered by this reflection paper.
1.	Adaptogens are reported to improve the quality of life (QOL), e.g. Eleutherococcus [Cicero et al., 2004; Narimanyan et al., 2005, etc.]	General aspect is addressed in the reflection paper. The study will be addressed in the AR of Eleutherococci radix.
2.	<p>The term adaptogen is derived from the term “Physiological adaptation” which is defined as a biochemical change in an organism that results from exposure to mild or moderate environmental stressors and generates a protective response against them. Such adaptive changes convey the organism from its normal steady state (homeostasis) to a increased level of dynamic equilibrium (heterostasis) or to the so-called state of non-specific resistance (SNSR) of the stress system.</p> <p>The term “adaptogen” was originally established by Lasarev, suggested that adaptogens are compounds which increase :</p> <ul style="list-style-type: none"> - “the state of non-specific resistance” of the organism, the so-called “adaptogenic effect”, and - working capacity after single and repeated administration (Lasarev, 1961, 1962; Brekhman and Dardimov, 1968). <p>SNIR is similar to “phase of resistance” of Selye’s “general adaptive syndrome” to stress, in term that it is generated in response to mild or moderate stressors (Lasarev 1962, Garkavi and Kvakina, 1986), but not in response to a strong stress. The repeated administration of adaptogens gives rise to an adaptogenic, or stress-protective, effect in a manner analogous to repeated physical exercise, leading to prolonged SNSR and increased endurance and stamina under extreme conditions (stress).</p>	<p>The HMPC is aware of the facts that are mentioned in the comment. Many of these aspects are addressed either in the reflection paper or in the assessment report for Eleutherococci radix.</p> <p>Reference to articles by Selye has been added.</p>

Paragraph no.	Comment and Rationale	Outcome
2. (Continuation)	<p>Three adaptive reactions generated in response to a stressor depending on the strength of the stressor were differentiated in sport medicine:</p> <ul style="list-style-type: none"> - reaction of training (in response to a mild stress), - reaction of activation (in response to a moderate stress) - stress-reaction (Selye's general adaptive syndrome in response to strong but not severe stress). <p>Alternatively, repeated small and medium doses of Eleutherococcus can induce adaptive reactions of training and activation (Garkavi and Kvakina, 1986).</p>	
2.	<p>A characteristic feature of adaptogens is that they act as eustressors or challengers (Panossian et al., 1999b). Thus, a single administration of an adaptogen mainly produces a challenging (stimulating or stress-agonising) effect (Nörr, 1993; Panossian et al., 1999b). It follows that the stress-protective effect achieved by multiple administration of adaptogens is not the result of inhibition of the stress response of an organism, but actually of adaptive changes in the organism as a response to the repeated stress-agonistic effect of the drug. In other words, using pharmacological terminology, adaptogens are stress-agonists and not stress-antagonists (Panossian et al., 1999b).</p> <p>In pharmacology, adaptogens can be defined as herbal medicinal products which can be used in case of decreased performance such as fatigue and sensation of weakness in order to increase resistance to physical, biological, chemical and psychological stresses.</p>	No changes. An extension of the indication for all "adaptogens" can not be supported by HMPC as substance-specific data would be necessary.
3.	<p>In fact, Brekhman proposed four characteristics of adaptogens. In addition to mentioned in EMEA document HMPC/102655/2007 there was one more – d)Effect of an adaptogen is as pronounced as deeper are pathologic changes in the organism (Brekhman, 1968)</p> <p>It should be noted that all these four characteristics has to be update, e.g. “almost non-toxic” for “wide therapeutic index”, etc.</p>	Agreed.

Paragraph no.	Comment and Rationale	Outcome
6.	The stimulating effect was defined as a single dose that increases work capacity. The tonic effect was defined as multiple doses that increase general well being and work capacity. (Brekhman, 1968)	Agreed.
8.	Effects of adaptogens are universal in sense of applying to any kind of organism ranging from the simple to the higher form: cells, simple organisms, invertebrates to mammalian [Boon-Niermeijer et al.2000, Chernikh et al., 1985].	Not endorsed. No studies for this very wide claim submitted.

4. Pharmacological studies in connection with the term adaptogen

Paragraph no.	Comment and Rationale	Outcome
1.	<p>The pharmacological assessment of adaptogens typically includes the evaluation of stimulating, tonic and stress-protective activities in model systems in which animals are subjected to various stress conditions, e.g. immobilisation [Lopez-Fando et al., 2004 ; Liu et al., 1996].</p> <p>It has been demonstrated that cortisol and nitric acid are appropriate markers that can be employed in the evaluation of the anti-stress effects of adaptogens, while only p-SAPK/p-JNK appears to be a potential marker in bioassays of adaptogens and presumably of potential antidepressants [Panossian et al., 2007]. <u>In general, pharmacological effect of adaptogens in stress is characterized by a decrease or total prevention of hormonal changes peculiar to stress</u> [Panossian et al., 2007]</p> <p>Effects of adaptogens are mainly associated with the <u>hypothalamic-pituitary-adrenal (HPA) axis</u>, a part of the stress system that is believed to play a primary role in the reactions of the body to repeated stress and to adaptation by balancing the releases of adrenaline (the “switch-on” hormone), <u>corticosteroids</u> (the feed-back regulatory “switch off” hormones that protect an organism from overreaction), and nitric oxide (that modulates the biosynthesis and effects of many hormones and autacoids, and plays a role in the nervous, cardiovascular, immune, gastrointestinal and endocrine systems) [Panossian et al., 1998.1999]. The effects of adaptogens on HPA axis [Filaretov et al., 1986; Gaffney at al., 2001; <u>Kimura and Sumiyoshi</u> , 2004], nitric oxide [Panossian et al., 1999; Lee et al., 2004 ; Huong et al., 2005; . Achike and Kwan 2003; Chen et al., 2003; Scott at al., 2001; Kim et al., 1998, 2003; Iuvone et al., 2003] and eicosanoids [Panosyan et al., 1988; Ohkura et al., 1990; Bu et al., 2005; Park et all., 2005] and stress activated protein kinases (SAPK/Jun) are well documented.</p>	<p>The level of details exceeds the scope of the reflection paper. The relevant studies will be addressed when the related herbal substances will be assessed.</p> <p>The reflection paper may be updated, if the need arises from the assessment of other herbal substances with adaptogenic properties.</p>

Paragraph no.	Comment and Rationale	Outcome
1. (Continuation)	<p>Adaptogens were found to act on the hypothalamus and/or hypophysis primarily, and stimulated ACTH secretion 30, 60 and 90 min after single oral or intraperitoneal treatment [Hiai et al., 1979], which resulted in increased synthesis of corticosterone in the adrenal cortex, increased plasma corticosterone [Hiai et al., 1979; Filaretov et al., 1988], and in the increase of a working capacity up to 132% [Filaretov et al., 1988]. Effect of repeated administration (seven-day) for more intensive (179%), but surprisingly without any changes of cortisone level in blood [Filaretov et al., 1988]. It was found that ginseng saponins would be a kind of mild stressful agents [Hiai et al., 1979; Kim et al., 1998; Filaretov et al., 1988];</p> <p>Kim et al., 1999; Kim et al., 2003], which adapt the organism to stress (e.g. completely antagonized cold water swimming induced immunosuppression Luo et al., 1993) and attenuate stress (immobilization, intracerebroventricular injection, heat, cold water swimming, morphine) induced elevated corticosteroids level in blood [Kim et al., 2003; Kim et al., 2003; Luo et al., 1993; Yuan et al., 1989] presumably by blocking ACTH action in the adrenal gland [Kim et al., 2003;] and by inducing NO production in the brain [Kim et al., 1998]. In addition Ginseng saponins affects brain monoamines decreasing stress induced increase of noradrenaline and serotonin in heat-stressed mice, Similar effects on HPA axis in normal conditions and stress were obtained in experiments with another tetracyclic triterpene glycoside - cucurbitacine R diglucoside, an active principle of Bryonia alba, producing stress protective and stimulating effect in animals [Panossian et al., 1998; 1999].</p> <p>Repeated administration of an adaptogen produces a stress-protective effect, in a manner analogous to that occasioned by repeated physical exercise, and may generate a prolonged SNSR together with increased endurance and stamina under extreme conditions (Dardymov, 1976; Lupandin and Lapajev, 1981; Viru, 1981; Saratikov and Krasnov, 2004; Korolevich and Lupandin, 1967; Levchenko, 1971; Lapajev, 1982; Lupandin, 1990; Bucci, 2000). The beneficial effect of repeated treatment with adaptogens is mainly evident in patients suffering from chronic disease or a disturbed state (Krasik et al., 1970a, b; Lebedev, 1971; Lapajev, 1978; Lupandin and Lapajev, 1981; Mikhailova, 1983; Panossian et al., 1997; ESCOP Monographs, 2003a, b; Saratikov and Krasnov, 2004).</p>	

Paragraph no.	Comment and Rationale	Outcome
1. (Continuation)	<p>It has been recently demonstrated that the standardised extract SHR-5 from <i>Rhodiola rosea</i> possesses a significant anti-depressive activity in patients suffering from mild to moderate depression [Darbinyan et al., 2006]. Earlier curative effect of Schizandra in patients with aesthetic and depressive syndromes was shown [Staritsina 1946, Sivertsev 1946; 1950; Leman 1952; Galant et al. 1957; Galant, 1958; Zakharov, 1956; Romas, 1958; 1967].</p> <p>Repeated administration of an adaptogen produces a stress-protective effect, in a manner analogous to that occasioned by repeated physical exercise, and may generate a prolonged SNSR together with increased endurance and stamina under extreme conditions (Dardymov, 1976; Lupandin and Lapajev, 1981; Viru, 1981; Saratikov and Krasnov, 2004; Korolevich and Lupandin, 1967; Levchenko, 1971; Lapajev, 1982; Lupandin, 1990; Bucci, 2000).</p> <p>The beneficial effect of repeated treatment with adaptogens is mainly evident in patients suffering from chronic disease or a disturbed state (Krasik et al., 1970a, b; Lebedev, 1971; Lapajev, 1978; Lupandin and Lapajev, 1981; Mikhailova, 1983; Panossian et al., 1997; ESCOP Monographs, 2003a, b; Saratikov and Krasnov, 2004). It has been recently demonstrated that the standardised extract SHR-5 from <i>Rhodiola rosea</i> possesses a significant anti-depressive activity in patients suffering from mild to moderate depression [Darbinyan et al., 2006]. Earlier curative effect of Schizandra in patients with aesthetic and depressive syndromes was shown [Staritsina 1946, Sivertsev 1946; 1950; Leman 1952; Galant et al. 1957; Galant, 1958; Zakharov, 1956; Romas, 1958; 1967].</p>	

Paragraph no.	Comment and Rationale	Outcome
3a	<p>Adaptogens by definition can enhance the “state of non-specific resistance” of an organism to stress . This implies that they can act in the organism on different levels of regulation of adaptation to physical, chemical, biological and sociological stress factors, associated with the activity of the nervous system (CNS and sympathetic), the endocrine system [hypothalamus-pituitary-adrenal (HPA) axis) as well as the innate immunity, i.e. the activity of the non-specific immune system (antimicrobial enzyme system, non-specific cytokines, complement system, phagocytic and NK cells).There are many publications where antiviral, immunostimulant, anti-inflammatory and antibacterial effects of Eleutherococcus was demonstrated (Lin et al., 2007; Glatthaar-Saalmüller et al., 2001 etc; Zhu et al 1982; Schmolz et al. 2001; Steinmann et al., 2001; Kimura and Sumiyoshi , 2004).</p> <p>Eleutherococcus senticosus has been demonstrated to have pronounced effects in common colds and influenza like diseases</p>	<p>The HMPC is aware of the facts that are mentioned in the comment. Many of these aspects are addressed either in the reflection paper or in the assessment report for Eleutherococci radix.</p>
3b	<p>General purpose of adaptogens is prolongation of the of the phase of non-specific resistance of stress response (general adaptive syndrome) and the reduction of stress reaction by reduction of sensitivity(reactivity) to stress Depending on the individual level of reactivity of an organism (homeostasis) to a stressor , the adaptive response to mild, moderate or strong stress is quite different, inducing as a result quite different reactions of adaptation (training, activation and stress). Repeated small and medium doses of Eleutherococcus can induce adaptive reactions of training and activation (Garkavi and Kvakina, 1986). The repeated administration of adaptogens gives rise to an adaptogenic, or stress-protective, effect in a manner analogous to repeated physical exercise, leading to prolonged SNSR and increased endurance and stamina under extreme conditions (stress) Brechman, 1961.</p>	

5. Pharmacodynamic action and clinical data

Paragraph no.	Comment and Rationale	Outcome
1	<p>Detailed and intensive study of <i>Eleutherococcus senticosus</i> was started in Far East division of USSR Academy of sciences in end of 50th of last century. And a first medicinal preparation in form of liquid extract of roots of <i>E. senticosus</i> was produced in Khabarovsk chemical pharmaceutical factory in 1964. This product very quick becomes popular. About 1000 ton of extract per year was produced and exported in 15 countries in the beginning of 80th of last century (Zhuravlev & Kolyada, 1996).</p> <p>According to Dardymov & Khasina (1990) preparations of <i>E. senticosus</i> posses:</p> <ul style="list-style-type: none"> - energomobilized effect be means of intensive utilization of glucose; - stress-protective effect by regulation of central nervous system and hormonal regulation; - effects on hormones and its mediators including deviation of cyclic nucleotides and prostaglandins. <p>The interest to clinical effects of adaptogenes increased dramatically and these effects are well documented. Grinevich (1970) and Yaremenko (1990) have reported about application of <i>Eleutherococcus</i> in complex therapy of oncological patients. <i>Eleutherococcus</i> have prevent induction and grafting of tumors, help in decrease of number of metastases.</p> <p><i>Eleutherococcus</i> was recommended for treatment of combustion traumas of eyes (Smoljakova et al., 1991). Treatment of patients with neuroses during 3-4 weeks resulted in positive effects mainly in decreasing of vegetative dystonia. Administration of <i>E. senticosus</i> by patients in presurgery period promote quicker reconvalescence period (Sokolov, 2000). A clinical trial was undertaken to investigate the effects of <i>E. senticosus</i> (ES) and <i>Panax ginseng</i> (PG) on competitive club-level endurance athletes engaged in their normal in-season training. Participants were matched for training stress and received a 33% ethanolic extract (8 mL/day) containing either ES, PG (equivalent to 4 g and 2 g/day of dried root, respectively), or a placebo. ES increased rather than decreased hormonal indices of stress, which may be consistent with animal research suggesting a threshold of stress below which ES increases the stress response and above which ES decreases the stress response (Gaffney et al., 2001).</p>	<p>The HMPC is aware of the facts that are mentioned in the comment. Many of these aspects are addressed either in the reflection paper or in the assessment report for <i>Eleutherococci radix</i>.</p> <p>The respective article of Smoljakova et al, 1991 has not been assessed because it is in the VINITI deposit and not accessible.</p>

Paragraph no.	Comment and Rationale	Outcome
1.	<p>The study by Facchinetti et al. (2002) demonstrated that treatment with <i>E. senticosus</i> is able to reduce cardiovascular responses to stress in healthy young volunteers, while placebo was ineffective. <i>E. senticosus</i> is confirmed to be helpful for stress adaptation.</p> <p>The effect of a middle term <i>E. senticosus</i> administration on elderly, health related quality of life was tested in a double –blind placebo controlled experiment on 20 elderly hypertensive and digitalized volunteers (age ≥ 65 years). It was established that <i>E. senticosus</i> safely improves some aspects of mental health and social functioning after 4 weeks of therapy, although these differences attenuate with continued use (Cicero et al., 2004).</p> <p>Similar experiments were performed for other adaptogenes (Medvedev 1963; Darbinyan et al., 2000; Kurkin et al., 2003; Panossian 2003; Saratikov & Krasnov, 2004; Panossian & Wagner, 2005).</p> <p>Detailed mechanisms of activity of adaptogenes still unknown. <i>R. rosea</i>, <i>S. chinensis</i> and <i>E. senticosus</i>, all contain relatively high amounts of phenolic compounds, particularly phenylpropane or phenylethane derivatives. These compounds are structurally related to the catecholamines, and presumably play important roles in the SAS and CNS systems.</p> <p>In contrast, plants such <i>P. ginseng</i>, <i>E. senticosus</i> etc, which contain relatively large amounts of tetracyclic triterpenes that are structurally similar to corticosteroids, reveal their stress protective effects and adaptation to stressors after repeated administration for periods of 1–4 weeks. In these cases, the active components play key roles in the HPA axis-mediated regulation of the immune and neuroendocrine systems (Panossian & Wagner 2005).</p>	See above.

5.1. The role of adaptogens in Phytotherapy

Paragraph no.	Comment and Rationale	Outcome
1.	<p>Addaptogens and quality of life (QOL).</p> <p>It has been suggested that adaptogens could be useful in improving the quality of life of subjects. It can also be anticipated that adaptogens will have a direct impact on many factors that may be indirectly important in a number of social and environmental areas, table 1. [Narimanian et al., 2005].</p> <p>When implemented as adjuvants in the standard therapy of many chronic diseases and pathological conditions, adaptogens have been shown to be useful in improving the quality-of-life of patients. For example, adjuvant therapy with ADAPT-232 has a positive effect on the recovery of patients suffering from acute non-specific pneumonia. In a double-blind, placebo-controlled, randomised, phase III study, ADAPT-232 decreased the duration of the acute phase of the illness, increased mental performance of patients in the rehabilitation period, and improved their quality-of-life. With respect to all quality-of-life domains (physical, psychological, social and ecological), patients in the ADAPT-232 group scored higher at the beginning of the rehabilitation period, and significantly higher on the fifth day after clinical convalescence, than patients in the control group. [Narimanian et al., 2005].</p> <p>Effect of <i>Eleutherococcus senticosus</i> Maxim. on quality of life in elderly hypertensive and digitalized volunteers has been demonstrated in a randomized clinical trial after 4 weeks of therapy. <i>E. senticosus</i> safely improves some aspects of mental health and social functioning after 4 weeks of therapy, although these differences attenuate with continued use [Cicero et al., 2004], probably as a result of adaptation to treatment.</p> <p>A series (n=9) of double-blind, placebo-controlled trial, randomized clinical trial of <i>Panax ginseng</i> extract on quality of life demonstrated some degree of QoL improvement (in 8 studies). Thus, it was demonstrated that Pharmaton Capsules, taken for 12 weeks, were more effective than the multivitamin capsules alone in improving the quality-of-life in a population (625 patients) subjected to the stress of high physical and mental activity. By the end of the study, the 4th of the monthly assessments showed that both the group-A and the group-B treatments had induced a significant increase in the quality-of-life index, the change being 11.9 points for Pharmaton Capsules in group A which was significantly superior to the 6.4 average increase with the group-B capsules containing multivitamins alone [Caso Marasco et al., 1996].</p>	<p>The HMPC is aware of the facts that are mentioned in the comment. Many of these aspects are addressed either in the reflection paper or in the assessment report for <i>Eleutherococci radix</i>. It should be noted that the assessment of QoL must be based on validated instruments that take into account the condition of health/disease and cultural aspects. The general methodological issues relating to clinical trials with adaptogens, that were assessed by HMPC until now, i.e. <i>Eleutherococcus</i>, are of particular importance for QoL studies.</p>

Paragraph no.	Comment and Rationale	Outcome
1. (Continuation)	<p>A randomized, multicenter, double-blind, parallel group study was performed to assess the effects of a standardized ginseng extract compared with those of a placebo on quality of life (QoL) and on physiological parameters in 384 symptomatic postmenopausal women. With regard to the primary endpoint (total score of the PGWB index) the extract showed only a tendency for a slightly better overall symptomatic relief ($p < 0.1$). Exploratory analysis of PGWB subsets, however, reported p-values < 0.05 for depression, well-being and health subscales in favor of ginseng compared with placebo [Wiklund et al., 1999].</p> <p>Beneficial effects of Ginseng were evident in all studies within instrument summary component scores but improvement in overall composite scores of QoL was rarely seen. However, findings were equivocal. While populations evaluated varied in terms of underlying morbidity, there did not appear to be a substantial difference in their response to ginseng with respect to QoL. Despite some positive results, improvement in overall health-related quality of life cannot, given the current research, be attributed to <i>P. ginseng</i>. However, the possibility that various facets of QoL may have improved and the potential of early transient effects cannot be discounted [Coleman et al., 2003].</p> <p>Considering all of the above, it can be suggested that adaptogens have not only specific therapeutic effects in some stress-induced and stress-related diseases, but also have an impact on the quality of life of patients when implemented as adjuvants in the standard therapy of many chronic diseases and pathological conditions (post-surgery recovery, asthenia, congestive heart failure, chronic obstructive pulmonary disease, type II diabetes, cancer, epilepsy, etc).</p> <p>Table 1. The presumed affects of adaptogens on quality-of-life domains</p> <p>QoL domains: Effects of adaptogens</p> <p><i>Physical Health Domain:</i> Effects on endocrine, immune and CNS system</p> <p><i>Energy and fatigue:</i> Stimulating, anti-fatigue effect in asthenia and healthy subjects</p>	

Paragraph no.	Comment and Rationale	Outcome
<p>1. (Continuation)</p>	<p><i>Work capacity:</i> Increasing physical and mental working capacity</p> <p><i>Dependence on medicinal substances and medical aids:</i> Increasing resistance on an organism in stress; prophylactic effect to infections</p> <p><i>Activities of daily living:</i> Stimulating mental and physical performance</p> <p><i>Mobility:</i> Stimulating effect</p> <p><i>Sleep and rest:</i> Normalising sleep effect</p> <p><i>Pain and discomfort:</i> Anti-inflammatory effect</p> <p>Psychological Domain: Effects on CNS system</p> <p><i>Thinking, learning, memory and concentration:</i> Increasing mental performance (thinking, learning and concentration)</p> <p>Negative and positive feelings</p> <p>Positive effect in patients with psychogenic depression, astheno-depressive states, schizophrenia and alcoholism</p> <p><i>Self-esteem</i></p> <p>See above</p> <p>Social Relationships Domain Effect on stress system (neuroendocrine –immune complex)</p> <p><i>Sexual activity</i> Increasing libido and male fertility</p>	

5.2. Preclinical and clinical data

Paragraph no.	Comment and Rationale	Outcome
5.	<p>Pharmacokinetic of tritium labelled Eleutheroside B is well investigated in several studies (Bezdetko et al., 1981; 1982; Barenboim et al., 1986; German et al., 1982)</p> <p>Research has demonstrated standardized extracts of E. senticosus at generally recommended dosages do not significantly alter the metabolism of medications dependent on the cytochrome hepato-de-toxification pathways, CYP3A4 or CYP2D6 (Donovan et al., 2003).</p>	<p>The HMPC is aware of the facts that are mentioned in the comment. Many of these aspects are addressed either in the reflection paper or in the assessment report for Eleutherococci radix. HMPC raised methodological concerns on the interaction studies. For traditional use medicines Pharmacokinetic properties are not required as per Article 16c(1)(a)(iii) of Directive 2001/83/EC as amended.</p>
6.	<p>The conclusion that clinical studies have a number of shortcomings such as deficiencies in the description of the inclusion and exclusion criteria, description of medication, diagnosis, study design, analysis etc. is partially true, but there are some well performed studies (evidence type Ib, IIa of EMEA classification), e.g. see below, pages 10,11. Careful reading of original articles in Russian reveals that almost all of cited studies have placebo control, are single or double blind, randomised (because of statistically insignificant difference between control and verum groups at the beginning of the study) , and with large number of observations. Usually they are One group subject receiving all test articvles (including placebo) after wash out period for every patient Below we enclose the list of publications which can be analysed for their scientific merits. As about preparation used in Russian studies it should be mentioned that Russian scientists mainly used in their studies a preparation available in USSR – the extract (DER_{genuine} 1:13, DER_{total} 1:1) produced in Khabarovsk chemical-pharmaceutical factory (the only producer of this preparation in USSR in 60-80) which is described in details in the paper of Seledtsev IN, Skvortsova NA. Industrial production of medicinal products from roots of Eleutherococcus senticosus. In: Results of studies of Eleutheropoccus in Soviet Union. Ed. Brekhman II, Siberian Department of USSR Acad Sci. Vladivostok, 1966, pp. 23-24. Only in 1965 the 13 tons of the extract (130 000 bottles of 100 ml) and 2500 packages of tablets of Eleuterococcus extract was produced at this factory (Seledtsev and Skvortsova, 1966). It should be mentioned that insignificant difference between placebo and treatment groups find out in some clinical trials in athletes, e.g. Dowling et al..1995, is due to adaptogens are effective only at static and short dynamic loads.</p>	<p>HMPC is well aware on the issues relating to the interpretation of old studies and published literature. Specific guidance addresses the approach taken by HMPC in the assessment of these refernces. The fact that the term "adaptogen" and the use of adaptogens is widely accepted in many countries originating from the former Soviet Union whereas it is not accepted in many EU Member States makes a balanced assessment particularly difficult. Even though the Rapporteur had, in the case of Eleutherococcus, access to many articles in Russian language, many details of the studies were not accessible. A more detailed assessment would require bibliographies in English language. Some information seems to be intentionally disclosed by the authors for reasons mentioned in the comments submitted. These issues add to the more fundamental problem of the pharmacology of "adaptogens".</p> <p>The reflection paper presents the current thinking of HMPC. It may be updated in the light of additional information that may be obtained when assessing other herbal substances with adaptogenic properties.</p> <p>At present it contributes to the assessment of Eleutherococci radix that is reflected in the Community herbal monograph and proposed list entry.</p>

Paragraph no.	Comment and Rationale	Outcome
6. (Continuation)	Thus, Eleutherococcus has significant effect at static physical load, e.g. in heavy lifters and gymnasts exercising with static loads, Eleutherococcus is still significantly active for dynamic loads of maximal power for short periods of time (30 seconds on veloergometer), however it does not have any effect on working capacity of athletes when they have long-lasting heavy dynamic load, e.g. for three min. of veloergometry (Blokhin, 1966).	
6.	<p>Evidence type Ib, IIa of EMEA classification.</p> <p>Chronic fatigue A randomized, double-blind, controlled trial involving 96 patients with diagnosed idiopathic chronic fatigue evaluated the effectiveness of an Eleutherococcus extract compared to placebo. The extract was standardized to contain 2.24 mg eleutherosides per four 500-mg capsules (daily dose); 49 subjects received the herb and 47 received placebo. At the end of the two-month trial, 20 patients were lost to follow-up, leaving 76 evaluable subjects. After two months, a subset of subjects with mild-to-moderate fatigue demonstrated statistically significant improvement in Rand Vitality Index (RVI) scores compared to placebo. For the group as a whole, however, there was significant improvement in RVI scores at one month, but that improvement was not maintained for the duration of the study; after two months, RVI scores were not statistically different between treatment and placebo groups. These results might be expected, as adaptogens are not best suited to continual use but are typically more effective if given in a pulsed manner. Although this study used an imprecise, subjective measurement of fatigue, the results demonstrate a possible therapeutic benefit and additional studies are warranted (Hartz et al., 2004).</p> <p>Chronic stress In a double-blind study, 45 healthy volunteers (20 men, 25 women; ages 18-30) were randomized to receive two vials of Eleutherococcus senticosus or placebo for 30 days. Patients were subject to the Stroop Colour-Word (Stroop CW) test in order to assess their stress response, along with heart rate, and systolic and diastolic blood pressure, before and after treatment. Unlike placebo, those employing the herb had a 40-percent reduction in heart rate response to the Stroop CW stressor. Moreover, in females but not males, the use of Eleutherococcus accounted for a 60-percent reduction in systolic blood pressure response to the cognitive challenge test. These facts together suggest Eleutherococcus may be helpful for stress adaptation (Facchinetti et al., 2002)</p>	The AR on Eleutherococci radix has been updated. Differences between treatment groups were not statistically significant. It was concluded that overall efficacy was not demonstrated. However, the findings of possible efficacy for a subgroup of patients with moderate fatigue suggests that further research may be of value.

Paragraph no.	Comment and Rationale	Outcome
6. (Continuation)	<p>QOL and mental performance in acute inflammatory disease. A botanical combination comprised of Eleutherococcus senticosus (24.4%), Rhodiola rosea (27.6%), and Schisandra chinensis (51%) was investigated for its therapeutic benefit as an adjuvant to standard treatment in acute, non-specific pneumonia. In a double-blind, placebo-controlled, randomized trial, 60 patients (ages 18-65 years) received standard treatment consisting of cefazolin (antibiotic), bromhexine (mucolytic agent), and theophylline (broncho-dilator); 30 subjects also received the botanical combination and 30 received placebo.</p> <p>All medications were taken twice daily for 10-15 days and outcomes measured were duration of both antibiotic therapy and acute phase of disease, mental performance on a psychometric test, and self-evaluation for quality-of-life (QOL). Patients receiving the botanical combination required fewer days (5.67) of antibiotics than those in the placebo group (7.53 days), and also demonstrated a significantly higher level of performance on the psychometric tests. In addition, mean QOL scores in the treatment group were significantly higher than for those in the placebo group (Narimanyan et al., 2005).</p>	<p>We did not review a botanical combinations. Although the HMPC discussed the example of Eleutherococcus only, similar considerations may be necessary with other herbal substances with adaptogenic properties, including a botanical combinations..</p>
6.	<p>Immune deficiency</p> <p>In a controlled trial, 36 subjects were randomized to receive 10 mL Eleutherococcus senticosus root extract or placebo three times daily after meals for one month. A flow cytometric evaluation of lymphocyte subpopulations was made before and after administration of the herb or placebo. After four weeks of therapy, those in the active group had a significant increase in total lymphocyte (p<0.0001), T-helper (p<0.00001), T-suppressor (p<0.0001), natural killer (p<0.1), and B-lymphocyte (p<0.05) cells compared to placebo (Bohn et al., 1987)</p> <p>Athletic performance</p> <p>A single-blind, placebo-controlled clinical trial in six baseball players assessed the effects of a 33% ethanol root extract on maximal work capacity. Three maximal work tests using a bicycle ergometer were performed on 3 consecutive days prior to treatment, and two tests were carried out after treatment with either 2ml extract (containing 0.53mg syringin (eleutheroside B) and 0.12mg syringaresinol-4,-4-O-b-diglycoside (identified here as eleutheroside D)) or placebo orally twice daily for 8 days.</p>	<p>Study in human pharmacology; no clinical endpoint.</p> <p>The AR on Eleutherococci radix has been updated. The respective articles of Asano et al, 1986 and Arushanyan, E.B., Shikina, I.B., 2004 have already been assessed and included in the list of references. No changes in the reflection paper.</p>

Paragraph no.	Comment and Rationale	Outcome
6. (Continuation)	After each work test, maximal oxygen uptake, oxygen pulse, total work time and exhaustion time were measured. A significant improvement in all four parameters was observed in subjects treated with the extract ($P < 0.01$), including a 23.3% increase in total work time as compared with only a 7.5% increase following placebo treatment (Asano et al., 1986). Arushanyan, E.B., Shikina, I.B., 2004, "Improvement in light and colour perception in humans with prolonged use of eleutherococcus", <i>Experimental and Clinical Pharmacology</i> , 67, 4, pp 64-66. Garkavi, L.Kh., Shepelev, A.P., Tatkov, O.V., Mar'yanovskij, A.A., 2000, "Efficacy of Eleutherococcus and Kralonin in the treatment of patients with ischemic heart disease and neurocirculatory dystonia at health resorts", <i>Voenna-Med. Zhurnal</i> , 321, 9, pp. 42-47.	

6. CONCLUSION

Paragraph no.	Comment and Rationale	Outcome
1.	<p>The term adaptogenes is well recognized and common used by specialists and peoples. Just easy search by key-word "adaptogen" on www.google.com resulted in about 285 000 links in Internet. It should be clarified that in general adaptogenes improve the quality of life. The efficacy of adaptogenes is confirmed by hundred years of application in traditional medicine. In end of XX century and nowadays there is huge interest to adaptogenes and its effects. In fact some adaptogenic plants such as <i>Eleutherococcus senticosus</i>, <i>Panax ginseng</i>, <i>Rhodiola rosea</i>, <i>Schizandra chinensis</i> etc. are included in official Pharmacopoeia (USSR Pharmacopoeia, 11 ed., Japan Pharmacopoeia 15 ed., Ukrainian Pharmacopoeia 1 ed., European Pharmacopoeia 5 ed.). The concept of adaptogenes is sufficient to be considered in the officinal medicine.</p> <p>As a separate pharmacological group, adaptogens can be defined as it already suggested (Panossian and Wikman, 2007) as herbal medicinal products which can be used in case of decreased performance such as fatigue and sensation of weakness (as accepted by Swedish FDA) in order to increase resistance to physical, biological, chemical and psychological stresses.</p>	<p>See comments above. The concept of adaptogens is plausible and supported by many studies, although it is not recognized by official medicine in the EU. As stated by HMPC in the reflection paper, the studies presented and the concept of adaptogens deserve further clinical research.</p> <p>The reflection paper could be reviewed and even re-valued when new monographs would appear on the adaptogens such as <i>Rhodiola rosea</i>, <i>Schisandra chinensis</i>, <i>Rhaponticum carthamoides</i> etc.</p>