European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 12 January 2006
Doc. Ref. EMEA/381405/2005

OVERVIEW OF COMMENTS RECEIVED ON 'PUBLIC STATEMENT ON THE USE OF HERBAL MEDICINAL PRODUCTS CONTAINING SOYA OR PEANUT PROTEIN'

Table 1: Organisations that commented on the document as released for consultation

	Organisation
1.	Association of the European Self-Medication Industry (AESGP)

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Table 2:Discussion of comments

General comment	Comment and rationale	Outcome / Proposed change
	As previously communicated by the organisation commenting, it is believed that the proposed wording concerning soya oil is not totally adequate in view of the clinical experience and labelling requirements for food. The views are provided below in greater detail: <u>Clinical experience:</u> Soya oil is used as additive in oral forms in amounts of 50 to 300 mg/ dose unit which makes allergic reactions very unlikely, as confirmed by clinical experience. This is also confirmed by company data. With regard to the experience gathered with these products over many years, no real risk could be identified concerning the use of soya oil as an excipient. Therefore adding a warning is not really justified and would not add to the safe use of the product. On the contrary, it is feared that it may confuse or worry people and therefore impair compliance with a necessary treatment. We would like to note that the warnings concerning cross-reactions between soy and peanut are based on several cases of allergic reactions of teenagers with moderate asthma and peanut allergy after eating soy-containing food[1]. It is not all clear whether there are any documented cases of confirmed reaction with soya oil. Therefore we believe it is not appropriate to add such warnings on the package leaflet as they are only based on a theoretical risk.	The rapporteur agrees to the EFSA assessment, which does not offer new information in principal. It must be pointed out that EFSA refers only to bleached and deodorised oils, which indeed contain only very low amounts of residual protein, while the HMPC assessment addresses the general issue of protein content in plant oils used in medicinal products: „Soya and peanut products should be treated as allergenic unless they have an analytically-monitored non-allergenic specification and a safe maximum daily dose can be defined". Protein content and potential allergenicity depends on degree of refinement. For bleached and deodorised oils we agree with the AESGP that a limited labelling as proposed is sufficient, since no or only low allergenicity can be assumed. However, compliance to the European Pharmacopoeia does not guarantee that the quality of soya oil used in medicinal products meets these criteria in all cases. For this reason it is proposed that a limited labelling can be accepted only in those cases where a. the use of a bleached and deodorised oil is verified by an adequate specification which exceeds the demands of the soybean oil monograph and b. it is proven that the maximum daily oral intake according to the posology does not exceed 20 µg soy bean protein (see assessment report: Allergenic potency of medicinal products containing soy or peanut protein, revised version June 25, 2003). In the general case, when the specification only refers to the monograph and no adequate information on allergenicity is available, we recommend to maintain the more detailed labelling.

[1] Foucard T., Malmheden Y.L., A Study on Severe Food Reactions in Sweden – is soy an underestimated cause of food anaphylaxis? , Allergy 1999, 54, 261-265

	<u>Labelling requirements for food</u> Labelling of foodstuff with known allergenic potential is regulated by Directive 2000/13/EC as amended by Directive 2003/89/EC (newly introduced paragraphs 10 and 11). Food ingredients with known allergenic potential as listed in Annex IIIa of Directive 2000/13/EC, such as soybeans and products thereof, shall be indicated on the label with a clear reference to the name of this ingredient. The regular update of Annex IIIa of Directive 2000/13/EC is regulated by the newly introduced paragraph 11 which reads as follows: "*11. The list in Annex IIIa shall be systematically re-examined and, where necessary, updated on the basis of the most recent scientific knowledge. The first re-examination shall take place at the latest on 25 November 2005. Updating could also be effected by the deletion from Annex IIIa of ingredients for which it has been scientifically established that it is not possible for them to cause adverse reactions. To this end, the Commission may be notified until 25 August 2004 of the studies currently being conducted to establish whether ingredients or substances, derived from ingredients listed in Annex IIIa are not likely, under specific circumstances, to trigger adverse reactions. The Commission shall, not later than 25 November 2004, after consultation with the European Food Safety Authority, adopt a list of those ingredients or substances, which shall consequently be excluded from Annex IIIa, pending the final results of the notified studies, or at the latest until 25 November 2007.*	Analytical remarks Certain pharmaceutical forms such as soft gelatine capsules usually contain larger amounts of soy oil. The amounts used are up to 400 mg soy oil/capsule. A possible daily dosage up to 12 capsules would lead to a daily intake of 4,8 g soy oil (~ 5 ml soy oil), which may contain 20 ppb soy bean protein. These would equal ~ 4000 µg (4 mg) protein/l soy oil (4 ppm). For half of the dosage (6 capsules) or for a quarter of the dosage (3 capsules), the tolerable concentration would be 8 mg (8 ppm), and accordingly 16 mg (16 ppm) protein/l soy oil. An appropriate method should be able to measure proteins in soy oil in a range of approximately 1 – 50 ppm. Assessment 1) It is referred to the monograph 2.5.33 (Ph.Eur.) "Total protein". There are 7 methods for the determination of the proteins. Methods 2-6 are colorimetric methods. Method 1: measurement of the UV-absorption; detection limit: ~ 200 µg/ml. Method 2: "Lowry-assay"; detection limit: ~ 5 µg/ml. Method 3: "Bradford-assay" (Coomassie-stain); detection limit: ~ 2 µg/ml. Method 4: BCA-assay (bicinchoninic acis); detection limit: less than 5 µg/ml. Method 5: Biuret-assay; detection limit: above the detection limit of method 1. Method 6: fluorimetric method (OPA-assay); detection limit: less than 1 µg/ml. Method 7a: Kjehldahl-nitrogen-assay; detection limit: not reported, approx. 10000 µg/ml. Method 7b: total nitrogen determination after pyrolysis, Detection limit: not reported, approx. 10000 µg/ml.

	(….) *Where necessary, technical guidelines may be issued for the interpretation of the list in Annex IIIa, in compliance with the procedure referred to in Article 20(2).*" Following the procedure described in Article 11 of 2000/13/EC as amended (cited above), the European Food Safety Agency (EFSA) recently evaluated the allergenic potential and came to the conclusion "*that it is not very likely" that neutralised (alkali refined) bleached and deodorised (N/RBD) soybean oils* (which include neutralised bleached and deodorised soybean oil and fully refined soybean oil as well as hydrogenated soybean oil and fat and inter-esterified soybean oil and fat) *"will cause a severe allergic reaction in the majority of soybean allergic individuals*"[2]. As a result, refined soybean oil was included in the List of food ingredients and substances provisionally excluded from Annex IIIa of Directive 2000/13/EC, which is an annex of Directive 2005/26/EC[3]. In other terms, this means that refined soybean oil is exempted from being added to the label of food products.	In the literature a variation of the method 6 is described with the usage of a different reagent (ATTO-TAG CBQCA). The ATTO-TAG CBQCA reagent was originally developed as a chromatographic derivatisation reagent for amines. However, it is also useful for quantitating amines in solution, including the accessible primary amines in proteins. Some companies have developed a new kit that employs the ATTO-TAG CBQCA reagent for rapid and sensitive protein quantitation in solution. The CBQCA protein quantitation assay functions well in the presence of lipids and detergents, substances that interfere with many other protein determination methods. Detection of proteins with CBQCA is substantially more sensitive than OPA or fluorescamine and has a greater detection range (10 ng to 150 µg, for BSA). 2) Selective, chromatographic methods such as HPLC, which are generally suitable for the ppm-range, are not acceptable, because the selective detection of single proteins is not required and there might be problems with the detection limits. 3) Electrophoresis (Western-blot) is a specific and sensitive method, but is only useful for semi-quantitative determination.

[2] EFSA. Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to a notification from FEDIOL and IMACE on fully refined soybean oil and fat pursuant to Article 6 paragraph 11 of Directive 2000/13/EC (Request N° EFSA-Q-2004-098), adopted on 2 December 2004

3 Directive 2005/26/EC of the Commission of 21 March 2005 establishing a list of food ingredients or substances provisionally excluded from Annex IIIa of Directive 2000/13/EC of the European Parliament and of the Council

	Taking into account: - The situation in the food area, - The fact people with known soya allergy consults the list of excipients before taking any product, and - The fact that for people without known soya allergy, any reference to possible allergic reactions from soya oil will not add to the safe use of the product but instead may worry the patient and impair compliance with the treatment, it is believed that the labelling of medicinal products for oral use containing soya oil should be limited to the following information with regard to soya: - On the label: the name of the excipient - On the package leaflet, section 'contraindications': The general statement from the guideline on excipients (CPMP/463/00).	4) ELISA tests are widely used in the field of food analysis for the detection of allergenic compounds and can also be helpful in the field of medicinal products. Such tests, which detect Soya-IgA or IgG-antibodies, are known for their simple handling and high precision. A further benefit is that they are easy to quantify. However, the recovery rate is inversely proportional to the grade of heat processing of the sample material. That means, that in the case of soy bean protein the sensitivity might be decreased, because soy oil is heated up (approx. 200°C) (deodorisation). Therefore, these test kits are only of limited suitability for the discussed purpose because for such heat treated samples the test kits are not sensitive enough anymore. The detection limit of ELISA test kits is ~ 700 ppm, depending on the producer of the test. Sometimes even ELISA-test kits with a detection limit of 1 ppm are available. Whereas commercially available test kits for soya are not validated and most of them are developed for the detection of genetically modified soya, there are validated test kits for peanuts available. 5) The use of PCR methods does not seem to be suitable. The commercial kits from the field of food research, which are mostly based on PCR-gel electrophoresis, DNA-ELISA or Real-Time PCR have detection limits in the range of 10–100 ppm. However, the employment of DNA analysis in allergen detection is discussed controversially, since proteins are the allergenic component and PCR results cannot be linked to any allergen/protein content. Often there is only qualitative evidence on absence of DNA possible. A validated method is given in the § 35 LMBG (L-23.01.22-1): "Detection of a genetic modification of soybeans by amplification of the modified DNA sequence by means of polymerase chain reaction (PCR) and hybridization of the PCR product with a DNA probe", but it is to point out, that these methods have only been used for the determination of "RoundUP Ready®"-Soya so far. Therefore, the method should be modified for the intended use.

		In most of the cases in question, the proteins have to be removed from the oily phase by suitable methods such as liquid/liquid extraction, precipitation reaction and ultra filtration, because the detection can only be done in the aqueous phase. Methods for the removal of the proteins have been published. Within the aqueous phase the protein concentration increases and this might increase the detection limit. But there is no final evaluation to what extent this information can be confirmed in practice. It can be summarized that there are commercial test kids in the field of food-analysis available, which are based on fluorimetric methods, ELISA- or PCR-analytic and which may fulfil the requirements (detection range 1-50 µg/ml) under certain conditions. So the pharmaceutical companies are discharged from the additional development of new methods. Via combination with adequate preparation and enrichment steps, a detection limit within the low ppm-range might be achieved, see CREVEL et al.: Allergenity of refined vegetable oils (Food Chem Tox 2000). From the three methods stated above, the fluorimetric method should be favoured, because these method detects proteins selectively, it is easy to handle end the costs are not too high. However in any case the complete validation of the method used, including the sample preparation, is important and should be proven. The following wording was accepted to add in the chapter "Protein content in soya and peanut oil" after discussion in the HMPC: "Whereas validated methods for the protein determination in peanut oil exist, there is no validated methodology available for soy oil."