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Committee on Herbal Medicinal Products (HMPC)

Hearing AESGP during May 2012 MLWP meeting

Report

List of representatives from the Association of the European Self-Medication Industry (AESGP)

Christelle Anquez-Traxler, Werner Busse, Hubertus Cranz, Nand De Herdt, Marie-Laure Lacoste, Monica Mennet, Bernd Roether, Barbara Steinhoff.

The Chair of the Working Party on Community Monographs and Community List (MLWP) welcomed the AESGP delegation. Dr Cranz thanked the Chair and the MLWP for the opportunity to discuss issues related to the scientific assessment of plants and the development of Community Monographs (CM) and List entries with the MLWP.

1. Dr Busse gave a presentation on the situation of traditional herbal medicinal products (THMPs) in Europe. In 2010 the **European market for herbal products** amounted to 6 billion euro. About 70% of the total sales of herbal products correspond to herbal medicines (either authorised or registered). The market is in constant growth but such growth varies from country to country.

   In terms of assessment, the review time for THMPs in Member States is also quite different from one country to another. It was also mentioned that the status of new THMPs is not harmonised within the EU as far as their sale status, distribution and pack sizes are concerned. The experience in registering existing or new traditional herbal medicines in a few EU countries was then presented in greater detail.

   The Chair of the EMA Committee on Herbal Medicinal Products (HMPC) thanked Dr Busse for the presentation on sales data of herbal products including countries' specific regulatory information but noted that the situation in each Member State is special and that members of the MLWP may have limited options to influence the particular situation.

   The Chair of the MLWP noted that it must indeed be difficult for medicinal products to remain competitive when competing against similar products with lower regulatory requirements. AESGP expressed the importance to maintain the sector competitive by e.g. having high-quality monographs with good indications or by ensuring the pragmatic handling of genotoxicity data.

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In response to a question on initiatives by AESGP, Dr Cranz mentioned among others a dialogue with the Heads of Medicines Agencies to ensure the proper and faithful implementation of the legislation, i.e. have CMs implemented without further restrictions. The main challenge is the competing regulatory system (food supplements), which is regulated by a different set of legislation. It may appear as more 'appealing' for not being subject to good manufacturing practices, pharmacovigilance, etc. as required by the legal framework for medicines. Dr Cranz emphasized that the work done by the MLWP members is very important but it needs to provide an interesting option. Unnecessary regulatory burden and inappropriate fees need to be avoided. He considered health claims and botanicals as the main current issue for the future of herbal products in Europe; a decision is awaited from the European Commission.

An MLWP member wondered whether pharmacovigilance for food supplements could be an option. Dr Cranz responded that, by definition, food is safe but the definition of food supplements is being subject to different interpretation in some countries and hence some food supplements require warnings, etc. However, if a plant has safety concerns, it should be a medicine and not a food.

2. Dr Christelle Anquez-Traxler presented the results of the **2012 AESGP survey** on key performance indicators with regard to herbal medicinal products (HMP) which had been conducted amongst AESGP members. The survey is a follow-up to the 2011 survey presented last year to the MLWP. Data was collected on assessment time, fees, level of openness and accessibility of authorities, reference to CM, etc. Given a total of only 73 responses (less than 2011) AESGP acknowledged that for some countries the data were limited and did not allow robust conclusions. According to this survey, CM were used in 40% of applications and in the great majority of cases, the SmPCs were fully in line with the CM. Fees remain quite diverse across the EU. AESGP members found that proportionate fees, short review timelines, and assessment with HMP expertise (such as on particularities of HMP in genotoxicity testing) would be major incentives to use the registration system. Openness and accessibility of authorities before and during the procedure were found quite satisfactory.

   On the issue of genotoxicity, the Chair of the MLWP informed that an HMPC assessors' training non-clinical safety assessment including genotoxicity had taken place in 2010. In addition the Committee is committed to making progress on this issue and has asked industry for a collaborative approach making reference to the introduction of the bracketing and matrixing principle in herbal-specific genotoxicity guidance and a hearing with Kooperation Phytopharmaka organised in 2010.

3. On the general functioning of the MLWP, AESGP expressed its satisfaction with the **quality of CM**, the level of the indications and the general development process. AESGP endeavours to provide sound and quality comments on the monographs and hence appreciated cases where comments are reflected and lead to a revision of the monograph.

   For example the CM on *Arctostaphylos uva-ursi*, folium was reconsidered following AESGP complaints on the change of indication. Although, there was no final change to the CM, AESGP appreciated the consequent strategy of the Committee to reopen the assessment and also to amend their procedure in case of a major change between the draft and final CM. As another example the CM on *Plantago lanceolata* was mentioned, for which the MLWP took into account AESGP comments on the package leaflet and dosage for children.

   AESGP also appreciated the increased transparency in the release of HMPC opinions and the possibility to identify the nationality of the authors of minority opinions. This indication is important for companies when preparing their registration strategy.

Asked for the possibility of re-assessments e.g. for substances having a public statements as outcome, the MLWP confirmed that this is in principle possible in line with recently issued guidance on the timelines and revision of monographs if justified by new data. The same applies to final scientific assessment.

A specific question was asked with regard to the HMPC Regulatory Q&A # 8 in particular on monographs referring to a liquid extract and its applicability to a dry extract. It was explained that for a liquid extract containing a number of essential oils, the dry extract could be very different; subsequently there is no automatic transfer from a liquid to a dry extract. However, it was confirmed that Q&A # 8 offers the option to apply the content of a monograph describing a liquid extract for a dry extract, if this is sufficiently justified in the application or the experts' report.

AESGP and MLWP discussed the future priorities for CM and the potentially desirable total number. AESGP highlighted the importance of optimum quality CM covering the important plants from a business and market perspective, which is a goal that is nearly reached by the MLWP at the moment. AESGP will suggest a couple of plants for CM but is overall satisfied with the number of CM being issued. The MLWP informed that according to the HMPC work programme re-prioritisation is currently initiated under involvement of National Competent Authorities.

4. With regard to common traditional **combination products** it was confirmed that the proof of tradition relates always to the specific active substance, either a single herbal substance/preparation or a combination. CM can be used as supportive documents when putting together an application for a combination of plants not covered by a monograph on that specific combination; however there is no automatic transferability.

5. AESGP asked for developments on the approaches proposed in the Reflection paper on the necessity of initiatives to stimulate the conduct of **clinical studies with HMP in the paediatric population**. It contains proposals to develop a list of herbal substances with a benefit in children in partnership with the EMA Paediatric Committee (PDCO) and the promotion of funding to collect more data on monitoring the safe use in children and to promote further research. The MLWP confirmed some interest from paediatricians in the PDCO as well as that a list of herbal substances could be beneficial; however it is difficult to predict when such a list may be available. The worksharing exercise under Articles 45 and 46 of the paediatric regulation was also mentioned as potential source for existing paediatric data but no new data are expected out of this review. Collection of data, e.g. from public pharmacies could be supportive. The new European research and funding programme 'horizon 2020' may prove a suitable environment to advocate for more research in the field of paediatric use of herbal medicines.

6. The EMA has published for consultation a draft **list of European Union reference dates** (referred to as the 'EURD list') for periodic safety update reports (PSURs) in preparation for the introduction of the new pharmacovigilance legislation in July 2012. The EURD list contains 3155 active substances, including herbals. AESGP asked about the reasons why these plants were included into the list and for the chosen dates for submission. The MLWP responded that the originally much longer list was based on existing EudraVigilance databases and was a mixture of herbal medicinal products with other product categories (including homeopathic medicines). The MLWP/HMPC pragmatically reduced and corrected to a reasonable degree based on safety concerns. The EU reference dates are usually chosen in line with the first registration/authorisation of the first medicinal product containing the active substance. Comments on the EURD list will be considered carefully.

The hearing was closed and all participants agreed to continue the fruitful exchange on an annual basis with the option to organise an HMPC hearing if topics beyond details of MLWP assessment and CM establishment are discussed.