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Committee on Herbal Medicinal Products (HMPC)

AESGP remote hearing at HMPC meeting, November 2020

Report

List of representatives from the Association of the European Self-Care industry (AESGP)

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1. Pyrrolizidine alkaloids (PAs)

AESGP presented the results of the 2020 annual data evaluation on PA values found in herbal drugs and extracts as collected yearly by the German herbal industry. Since 2013 the problem of PA contamination represents a challenge for all parties involved which have been working together since then to find and apply interdisciplinary solutions. Results of the database show that a limit of 1.0 µg PA per day is considered appropriate to guaranty sufficient stability. On that note, AESGP expressed appreciation about the draft revision of the Public statement on the use of herbal medicinal products containing toxic, unsaturated pyrrolizidine alkaloids (PAs) including recommendations regarding contamination of herbal medicinal products with pyrrolizidine alkaloids with regards to the modified threshold of 1.0 µg. Replying to a question as to why 0.35 µg is not deemed possible, AESGP explained that over the years data have shown that the results come close to the threshold without never reaching it (asymptotic curve). The difference depends on the herbal drug themselves – plants that do not have an intrinsic PA issue at all but also plants that have an intrinsic PA issue. For herbal drugs and even more for herbal extracts a continuous reduction of the PA contamination can be observed over the years which shows a successful implementation of the mitigation solutions put into place. AESGP also looks forward to the publication of the new Ph. Eur. monograph on determination of PA contaminants.

AESGP then presented an overview on the current status of science on PA potencies as regards their toxicity. Differences regarding potencies of PA have to be taken into account and research has been progressing on this aspect. In 2016 it was proposed that PA could be grouped by structure and that relative potency are correlated to the structure and appear to span several orders of magnitude. EFSA have highlighted the need for more data in this area relating to toxicokinetic,

metabolic activation and genotoxic potency. Physiologically based Pharmacokinetic (PBPK) modelling is a state-of-the-art tool to bring in vitro data of this kind together to inform relative potency– based on estimates of amount of PA that reaches the target organ (the liver), correlated with measures of reactive metabolite formation in the liver cell. AESGP then emphasized that according to current scientific knowledge preliminary PBPK predictions show potency differences in diesters versus monoesters and PA versus its N-Oxide. Permeability in the gastrointestinal (GI) tract as well retro-conversion of N-Oxide under anaerobic conditions by gut microbes are relevant for the toxicokinetic and influence potency. The major site for PA metabolism is determined to be the liver and pre-systematic mammalian metabolism is not occurring to any appreciable degree in the GI tract. PBPK model predictions are verifiable using existing data and can be considered to give worthy predictions. Other data streams from other researchers are corroborating those findings and the research community continues to confirm that not all PA are created equals. A future workshop plans to align on potency factors and a new project towards aggregate PA exposure to inform realistic risk from all sources is envisaged. Industry are also willing to explore how to corroborate the risk assessment with an epidemiological investigation encompassing of a literature review and pharmacovigilance data.

2. Changes in Ph.Eur. monographs that lead to a change in declaration

This agenda item was discussed at the previous hearing in 2019; AESGP added it to the agenda to further clarify the extent of the issue caused by a change of methodology in the Ph. Eur. monograph not translated into the related EU monograph for standardised extracts. The Ph. Eur. monographs for Cassiae sennae leaves and fruits and extracts thereof are being revised to introduce HPLC as the new analytical assay method whilst photometry is the method referenced in the EU Sennae monograph. Standardised extract are declared as mg of active substance and the dosage is based on the active substance. If the monographs are not synchronized, then some batches analysed via photometric methods may be out of specification compared to HPLC. It is not possible to keep the product in line with EU monographs and Ph. Eur. and therefore AESGP recommends that the revision of the HMPC monograph be revised in line with the Ph. Eur. monograph. Although not optimal, calculating an average conversion factor (calculated based on the analysis of an important number of batches with the 2 methods) could be a pragmatic solution. This was indeed done for Horse chestnut. The HMPC promised to follow-up on this matter.

3. EU monograph indications repertory for ease of use

The publication of an overview of EU monographs in the form of Q&A in lay language is appreciated to increase their visibility and understanding by lay people. To further the use of monographs, AESGP suggested a search by indication with a link to the respective monograph and assessment report. An overall search function for indications which then lead to the respective monographs was considered useful but may not be so easy to establish. The point was recognized by the HMPC.

The HMPC thanked AESGP for its participation and hoped for a brighter 2021 and the return to face to face meetings. AESGP expressed its appreciation for the constructive discussion and thanked for the opportunity of this yearly exchange.