

## MEDICINES CONTROL AGENCY SYMPOSIUM

# Quality and safety at heart of new herbals directive

*The message that quality and safety are at the heart of the proposed new European directive on traditional herbal medicinal products (THMPD) was reinforced during a one-day symposium on traditional medicines and herbal remedies organised by the UK Medicines Control Agency (MCA) on November 27, 2002, in London. Dr Jo Barnes, lecturer in phytopharmacy at the School of Pharmacy, University of London, reports on the highlights*

Opening the meeting, RICHARD WOODFIELD, head of herbals policy unit, Medicines Control Agency, emphasised that herbal medicines are genuine medicinal products and summarised the reasons why the European directive on traditional herbal medicinal products is necessary,

First, it is difficult for manufacturers of herbal products to meet normal requirements for a full marketing authorisation (MA; product licence), particularly for efficacy.

Secondly, there are no requirements for quality and safety standards for herbal remedies sold as unlicensed products under the section 12(2) exemption of the Medicines Act 1968. As a result, there have been several important public health issues related to the use of certain unlicensed herbal remedies.

Thirdly, the current system does not provide a "level playing field" for manufacturers — effectively those who adhere to appropriate standards are likely to be disadvantaged on cost grounds and their reputations are at risk because of the activities of unscrupulous companies.

## RECENT AMENDMENTS

The key features of the proposed directive on traditional herbal medicinal products have previously been summarised (*P7*, 9 June 2001, p794). On 21 November 2002, the European Parliament voted to approve the directive while proposing several amendments, one of which was that the required minimum period of traditional medicinal use within the EU be reduced from 15 years to 10 years of the total requirement of 30 years. This amendment is supported by the MCA. Another proposed amendment is that products combining herbal ingredients and "nutrients" (ie, vitamins and minerals) should be permitted. This is also supported by the MCA, provided that any such remedies are genuinely traditional.

Referring to the timescale for implementation of the directive, Mr Woodfield said the best estimate is that it might be agreed in 2003 or 2004 and that EU member states would each have to set up their traditional HMP registration scheme by a specified date, possibly December 2004.

There will be a five-year transitional period during which manufacturers must ensure that their products comply with the provisions of the directive.

## QUALITY REQUIREMENTS

Under the directive, quality will be considered in relation to safety, rather than both safety and efficacy as with fully authorised conventional medicines, said Dr LINDA ANDERSON, principal pharmaceutical officer, MCA. Two specific sets of CPMP (Committee for Proprietary Medicinal Products) guidelines as well as other relevant guidelines (available from the European Medicines Evaluation Agency website, [www.emea.eu.int/](http://www.emea.eu.int/)) will apply:

- Quality of herbal medicinal products (CPMP/QWP/2819/00)
- Specifications: test procedures and acceptance criteria for herbal drugs, preparations and medicinal products (CPMP/QWP/2820/00)
- Points to consider on good agricultural and collection practice for starting materials of herbal origin (EMEA/HMPWP/31/99 Rev 3)
- Stability testing of existing active substances and related finished products (CPMP/QWP/122/02 [under revision])
- Impurities: residual solvents (CPMP/ICH/283/95)
- Validation of analytical procedures (CPMP/ICH/281/95 and CPMP/381/95)
- Regulations on TSE (transmissible spongiform encephalopathy) for excipients such as gelatin, magnesium stearate, stearic acid and lactose (EMEA/410/01 Rev 1)

## SPECIFICATIONS

In addition, the European Pharmacopoeia (Ph Eur), which contains over 120 specific monographs on herbal substances and general monographs on herbal drugs (herbal substances), herbal drug preparations and herbal teas, will also apply. Where a monograph for a herbal substance exists in the Ph Eur, this will be the minimum requirement with which manufacturers should comply. If a herbal substance is not included in the Ph Eur, manufacturers would have to draw up

their own specifications emulating the Ph Eur format, ie, definition, characteristics, identification (macroscopic, microscopic, chromatographic), tests (including foreign matter, loss on drying, total ash, etc), assay and additional tests such as pesticide and fumigant residues, microbial levels and mycotoxins. Similar specifications will also have to be produced for herbal drug preparations. Specifications for herbal medicinal products would need to include:

- Description
- Identity tests for each active substance
- Assay for known therapeutic constituents/markers
- Degradation products
- Tests specific to the dosage form, eg, hardness, uniformity of mass and disintegration tests for tablets

The pharmaceutical dossier that manufacturers would need to submit to the MCA to apply for a product registration under the directive is likely to be in a format similar to the common technical document (CTD) used for applications for marketing authorisations for conventional medicines.

Concluding, Dr Anderson advised manufacturers of herbal products that in the countdown to the directive, they should become familiar with the CPMP guidelines, Ph Eur, TSE regulations and the format of the CTD. Crucially, they should initiate stability studies for their products because these data are necessary in order to obtain a shelf-life for each product.

## QP, GMP AND INSPECTION

Under the proposed directive, the principles and guidelines of good manufacturing practice (GMP) for medicinal products for human use also apply (directive 91/356/EC), the detail of which is set out in the "Orange guide" (Rules and guidance for pharmaceutical manufacturers and distributors, London: Stationery Office; 2002), said BERNADETTE SINCLAIR-JENKINS, manager, policy and borderline unit, MCA. These include the requirement for manufacturers to have at their disposal at least one qualified person (QP) who has specific responsibilities for certifying the manufacture and release of batches. It is not necessary for the QP to be permanently

employed by a company — work on a contract basis is common — but he or she must have the appropriate educational qualifications and relevant experience required. Companies undertaking wholesale distribution must also comply with relevant legislation, for example, they are required to have at least one responsible person (RP) who must ensure that the relevant guidelines are complied with.

Manufacturers of products registered under the proposed directive will be subject to full inspections by MCA inspectors to ensure compliance with GMP standards, said IAN HOLLOWAY, senior inspector, inspection and enforcement division, MCA). This includes general quality assurance as well as guidance specifically for herbals (annex 7 of the “Orange guide” covers manufacture of herbal medicinal products). Mr Holloway invited manufacturers of herbal products to seek the MCA’s advice on plans and standards for manufacturing sites.

### PHARMACOVIGILANCE

Manufacturers of products registered under the proposed directive are required to comply with the provisions on pharmacovigilance set out in articles 101 to 108, inclusive, of directive 2001/83/EC, said LEIGH HENDERSON, scientific assessor, post-licensing division, MCA) Thus, manufacturers should:

- Have access to an appropriately qualified person responsible for pharmacovigilance at all times
- Have in place an adequate pharmacovigilance system to maintain detailed records of all suspected adverse drug reactions (ADRs) occurring worldwide
- Report to the licensing authority all serious suspected ADRs within 15 calendar days
- Include all other suspected ADRs as part of periodic safety update reports (PSURs)

Currently, only manufacturers of licensed herbal products are required to record and submit data on safety aspects to the MCA; manufacturers of unlicensed herbal products have no such obligation.

### PRODUCT INFORMATION

Another requirement that is relevant for the safety of products registered under the proposed directive is for manufacturers to include a package leaflet containing information on the product, said EMMA RADWAY-BRIGHT (post-licensing division, MCA). The leaflet must comply with standard leaflet requirements as set out in directive 2001/83/EC.

In addition, standard labelling requirements and those relating to advertising of medicinal products apply. Important with respect to herbal medicines is that advertis-

ing of products to the public should not claim that safety or efficacy are due to the fact that the product is “natural”.

### INDUSTRY PERSPECTIVE

ANTHONY BUSH, a health care consultant who was invited to give an industry perspective on the proposed directive, had several messages for manufacturers. The industry has to accept that the market is going to change and that the directive should be seen as an opportunity. The directive, which will allow manufacturers to make minor medicinal claims for their products, is an important step in helping the sector to grow. In addition, the directive would bring a secure regulatory home for unlicensed herbal products currently sold under section 12(2), and quality assurance would lead to consumer confidence and market credibility.

However, there are still some outstanding issues for the industry, such as the position of currently licensed herbal products, application fees and costs of complying with GMP and other requirements. He said that the directive is “very much a reality . . . [industry] planning for the future must be a top priority”. Concluding, Mr Bush asked what comes after the directive and how research into herbal medicines could be encouraged so that such products could take their rightful place in improving the health of the nation.

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