Regulatory Action and News

Herbal medicines: strengthening assessment methodology and improved communication

European Union — In 2012, the European Medicines Agency’s Committee on Herbal Medicinal Products (HMPC) adopted 15 Community herbal monographs and released seven monographs for public consultation. A total of 114 final monographs have been made available since the HMPC was established in 2004.

The monographs published to date cover a large number of therapeutic areas and the work plan of the HMPC for 2013 contains 30 draft or final monographs.

A Community herbal monograph comprises the HMPC’s scientific opinion on a given herbal substance and preparations thereof, based on the evaluation of all available scientific data and information on the historic use of these herbal ingredients in the EU vis-à-vis requirements of the legislation. The information contained in such monographs is used by Member States to support the evaluation of marketing applications from companies.

As part of the 2012–2015 work programme, the HMPC will look into strengthening its assessment methodology and aiming for continued high quality standards for its new or revised assessments. The first monographs having undergone systematic review/revision will be published in 2013.

The Agency has also started working on making the main information contained in the monographs as well as the studies and data used by the HMPC to issue its recommendations more accessible to the general public.

Patient and consumer organizations involved in the Agency’s activities have expressed strong support for this initiative which will represent a valuable source of information on the European view on herbal medicines and add to the vast amount of information released by the different national regulatory authorities on use of herbal medicines resulting from their scientific work within the EU network of medicines agencies.


Advanced therapies: incentives and strengthened interaction

European Union — In 2013, The European Medicines Agency’s Committee for Advanced Therapies (CAT) expects to review three or four marketing authorization applications (MAAs) for advanced-therapy medicinal products (ATMPs). This compares to three applications received in 2012, which led to the authorization for treatment of lipoprotein lipase (LPL) deficiency, a very rare inherited disorder.

While the number of MAAs for advanced therapies is still limited, an analysis of ATMPs under clinical evaluation published in 2012 in the journal Molecular Therapy shows that the research and development pipeline is large. This is confirmed by the amount of scientific advice provided to companies by the CAT and the number of ATMPs which have been classified.

Among the ATMPs under development, three quarters are cell-based medicinal
products while one quarter represents gene therapies. Products are being developed for cancer, cardiovascular diseases and haematology-related conditions.

In December 2012, the Committee published a reflection paper clarifying the legal basis of the classification of medicines as advanced therapies and provides information on how these medicines are classified as gene-therapy, somatic-cell-therapy, tissue-engineered or combined medicines. Some borderline cases and areas where scientific knowledge is limited or evolving rapidly are also discussed.

In 2012, 17 applications were submitted for a scientific recommendation on advanced-therapy classification. The CAT classified 14 of these as ATMPs, compared with the 12 submitted and 12 adopted in 2011. A similar number is expected in 2013.

As part of its work programme 2010–2015, CAT will continue to hold meetings on specific topics with interested parties such as scientific associations or trade organizations.


Methodologies in pharmacovigilance and pharmacoepidemiology

European Union — The PROTECT project, a public-private partnership for innovative methodologies in pharmacovigilance and pharmacoepidemiology, coordinated by the European Medicines Agency (EMA), has reached a crucial stage with the delivery of two databases which will offer access to important data resources for pharmacovigilance activities and pharmacoepidemiological studies.

The first of these two databases, the Drug Consumption Database, is a comprehensive and structured source of information on drug consumption in Europe. It is the result of reviewing, compiling and updating knowledge about European sources of data on drug utilization in out- and in-patient healthcare settings. Information is currently available for 17 EU countries (Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Spain, Sweden, and United Kingdom) up to October 2012. Work is in progress to expand data.

The second database, the PROTECT ADR database, is a listing of all ADRs contained in section 4.8 of the summary of product characteristics (SmPC) of medicinal products centrally authorized in the EU. It is based on the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The goal of this database is to improve the efficiency of the detection process of ADRs by allowing quick identification and filtering or flagging of listed and unlisted ADR. This database is updated every six months and currently contains information up to 30 June 2012.


Nicotinic acid/laropiprant: suspension recommended

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has confirmed the recommendation to suspend the marketing authorization for nicotinic acid/laropiprant (Tredaptive®, Pelzont® and Trevaclyn®) used to treat adults with dyslipidaemia. The CHMP decision follows the recent recommendation by
the Pharmacovigilance Risk Assessment Committee (PRAC) to suspend these medicines.

Doctors should no longer prescribe Tredaptive®, Pelzont® or Trevalyn® and should review patient treatment options.

A review of nicotinic acid/laropiprant was initiated in December 2012 after new data from a large, long-term study called HPS2-THRIVE became available. The results of the study, which are still preliminary, indicated that taking nicotinic acid/laropiprant together with a statin has no significant additional benefit in reducing the risk of major vascular events such as heart attack and stroke, compared with statin-alone therapy. In addition, a higher frequency of non-fatal but serious side effects was seen in patients taking these medicines.


**Mercury free healthcare**

Health Care Without Harm (HCWH) and the World Health Organization (WHO) are co-leading a global initiative to achieve virtual elimination of mercury-based thermometers and sphygmomanometers over the next decade and their substitution with accurate, economically viable alternatives. This initiative is based on the *Mercury in Health Care: 2005 WHO Policy Paper* which calls for short, medium and long-term steps to achieve the gradual substitution of mercury-based medical devices.

This project is a component of the UN Environment Programme’s (UNEP) Mercury Products Partnership, which is led by the US Environmental Protection Agency. This broader UNEP Products Partnership seeks action to eliminate mercury in products such as batteries, lighting and lamps, electrical and electronic devices, dental products, and measuring and control devices.

With specific regard to the WHO/HCWH Health Care collaborative initiative, the Products Partnership has set the objective of phasing out, by 2017, the demand for mercury-containing fever thermometers and sphygmomanometers by at least 70% and to shift the production of all mercury-containing fever thermometers and sphygmomanometers to accurate, affordable, and safer non-mercury alternatives.
UNEP has also been charged by the world’s governments to explore the possibility of establishing an international legally binding instrument to address mercury pollution.


Ocriplasmin: approved for vitreomacular traction

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended marketing authorization for Jetrea®, a medicinal product indicated for the treatment of adults with vitreomacular traction (VMT), an eye condition which can cause severe visual disturbance. This represents the first medicinal option for patients suffering from this condition.

The only active treatment option currently available for VMT is vitrectomy, whereby the vitreous humour is removed. The post-vitrectomy patient may have to undergo a period of four to six weeks without being able to work or live normally, out of which 7 to 14 days may be in a ‘head-down’ position to enhance the success rate of the surgical procedure. This ‘head-down’ posturing can be very inconvenient for the patient, and carries a significant burden of care to family or friends.

Jetrea® contains the new active substance ocriplasmin, a recombinant human protein derived from the yeast Pichia pastoris. Ocriplasmin has enzymatic activity against proteins in the interface between the vitreous humour and the retina. By breaking down these proteins, ocriplasmin can loosen the adhesion between the vitreous humour and the macula and can therefore resolve traction at the macula.


India: clinical trial conditions amended

India — The Ministry of Health has provided rules for granting permission and conducting inspections of clinical trials. Following notification of rules for providing compensation to victims of clinical trials, the Union Health Ministry has now amended the Drugs and Cosmetics (D&C) Rules to set conditions for giving permission to trials and inspection of sites.

The Government issued the notification to add a fresh rule (122 DAC) to the existing guidelines issued by the Drugs Controller General of India (DCGI) which lists all conditions for granting permission for clinical trials.

Schedule Y, requires adherence to good clinical practice guidelines and ethical research committee approval before initiating the study. It also makes trial registration mandatory within the Clinical Trials Registry of India before enrolling subjects. An annual status report of each clinical trial as to whether it is ongoing, completed or terminated must also be submitted to the licensing authority and in case of termination of any clinical trial, the detailed reasons should be communicated.

The notification also stipulates the need for reporting of serious adverse events during trials, rules for medical management of the injury during trials and reporting on compensation provided to victims. It also lays down rules relating to the inspection of sponsor premises, including their employees, subsidiaries, agents, contractors, sub-contractors and trial sites by authorized officers at any time with or
without prior notice. The officers will also have powers to search and seize any record, data, document, books, investigational drugs related to the trials.

The licensing authority may also impose any additional conditions for issuance of permission in respect of specific clinical trials, if considered necessary regarding the objective, design, subject population, subject eligibility, assessments, conduct and treatment of a clinical trial.

Actions that can be taken against the sponsors in the case of non-adherence to the rules are also specified. The licensing authority can repeal permission, debar the investigator and sponsors after giving warning letters in case any discrepancy is found during the inspections.


eSubmission Gateway release II and eSubmission web client

European Union — The European Medicines Agency’s (EMA) Gateway release II and eSubmission web client are now live for all applications for centralized procedure marketing authorization for human medicines.

Gateway release II is an upgraded version of eSubmission Gateway, the electronic submission channel that the Agency launched in 2012 to allow applicants to submit documents supporting all types of applications for human medicines to the EMA securely over the internet in the Electronic Common Technical Document (eCTD) format. The existing Gateway users will see new features in the system functionality such as an automated confirmation of the technical validation feedback to the applicant and an automated upload to the Agency’s eCTD review system.

As part of this project, the eSubmission web client, which complements the Gateway, is now available as well for applicants with lower transmission volumes. This web-based tool may be more suitable for small and medium-sized companies. Registered applicants can now start submitting all types of centralised procedure eCTD human applications through the web client.

Applicants who have registered and used the web client during the user acceptance testing can continue submitting their applications without further registration from 15 January 2013.

The EMA strongly recommends using Gateway or the web client for all eCTD submissions. Submissions on physical media (CD or DVD) will continue to be accepted as an alternative method for the time being. It is essential that applicants only use one method of submission as duplicate submissions might lead to negative technical validation and cause a delay in the processing of the application.


United States of America — The Food and Drug Administration (FDA) has expanded the approved use of Deferasirox (Exjade®) to treat patients aged 10 years and older for chronic iron overload in non-transfusion-dependent thalassaemia (NTDT).

NTDT is a milder form of thalassaemia that does not require individuals to get frequent red blood cell transfusions. However, over time, some patients with NTDT are still at risk for iron overload that damage vital organs.
The FDA is also authorizing marketing of FerriScan® as an imaging companion diagnostic for Exjade® therapy in patients with NTDT. The agency previously cleared FerriScan® for measuring liver iron concentration (LIC), but its use in Exjade® clinical studies to select patients for therapy, and to manage therapy, defined its role as a necessary imaging companion diagnostic. FerriScan® measures LIC non-invasively using magnetic resonance imaging.

Exjade® was previously approved for treatment of chronic iron overload due to blood transfusions in patients aged 2 years and older.


Pomalidomide approved for advanced multiple myeloma

United States of America — The Food and Drug Administration (FDA) has approved pomalidomide (Pomalyst®) to treat patients with multiple myeloma whose disease progressed after being treated with other cancer drugs.

Pomalyst® is intended for patients who have received at least two prior therapies, including lenalidomide and bortezomib, and whose disease did not respond to treatment and progressed within 60 days of the last treatment.

Pomalyst carries a boxed warning that the drug should not be used in pregnant women because it can cause severe life-threatening birth defects, and that the drug can cause blood clots. Because of the embryo-fetal risk, it is available only through the Pomalyst® Risk Evaluation and Mitigation Strategy (REMS) Programme.

Common side effects include neutropenia, anaemia, constipation, diarrhoea, thrombocytopenia, upper respiratory tract infections, back pain and fever.


Nalmefene approved for reduction of alcohol consumption

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended the granting of a marketing authorization for nalmefene (Selincro®), a medicinal product intended for the reduction of alcohol consumption in adults with alcohol dependence. Nalmefene is an opioid receptor antagonist.

Selincro® is indicated to help lower alcohol consumption in adults with alcohol dependence who have a consumption of more than 60 g of alcohol per day for males, and more than 40 g of alcohol per day for females, who do not have physical withdrawal symptoms and who do not require immediate detoxification.

The Committee also recommended that Selincro® should be prescribed in conjunction with continuous psychosocial support that focuses on treatment adherence and reducing alcohol consumption. The medicine should only be prescribed to patients who continue to have a high drinking risk level two weeks after initial assessment.


Mipomersen sodium and lomitapide approved for inherited cholesterol disorder

United States of America — The Food and Drug Administration has approved mipomersen sodium (Kynamro®) injection as an addition to lipid-lowering
medications and diet to treat patients with homozygous familial hypercholesterolemia (HoFH). The addition of Kynamro® helps to reduce low-density lipoprotein-cholesterol (LDL-C), apolipoprotein B, total cholesterol, and non-high density lipoprotein-cholesterol (non HDL-C).

In December 2012, the FDA also approved lomitapide (Juxtapid®) to reduce LDL-C, total cholesterol, apolipoprotein B, and non HDL-C in patients with HoFH.

HoFH, an inherited condition that occurs when the body is unable to remove LDL-C from the blood causing abnormally high levels of circulating LDL-C. For those with HoFH, heart attacks and death often occur before age 30.

The most common adverse reactions in the clinical trial included injection site reactions, flu-like symptoms, nausea, headache and serum transaminases.


Memantine: Imatinib mesilate: marketing authorization application withdrawal

European Union — The European Medicines Agency (EMA) has been notified by the manufacturer of its decision to withdraw the application for a centralized marketing authorization for the medicine imatinib mesilate (Ruvise®), 100- and 400-mg film-coated tablets. It was intended to be used for adults as add-on therapy for the treatment of pulmonary arterial hypertension (PAH).

The company has withdrawn the application since additional data are required to address CHMP questions relating to the benefit-risk assessment of imatinib in PAH patients. These data will not be available within the time-frame allowed in the centralized procedure.


Imatinib mesilate: marketing authorization application withdrawal

European Union — The European Medicines Agency (EMA) has been notified by the manufacturer of its decision to withdraw its application for centralized marketing authorization for the medicine memantine (Memantine FGK®), 7 mg, 14 mg, 21 mg and 28 mg, prolonged-release hard capsule. It was intended to be used for the treatment of patients with moderate to severe Alzheimer disease.

In its letter, the company stated that it is withdrawing the application for strategic reasons.