Regulatory Action and News

Helsinki Declaration: 2013 revision

The World Medical Association (WMA) has adopted and published a revised version of the Helsinki Declaration on biomedical research involving human subjects.

Delegates at the WMA’s 64th annual Assembly in Fortaleza, Brazil, voted overwhelmingly to support the changes which provide for increased protection for vulnerable groups involved in research and include a new provision for compensating people harmed as a result of participating in research. In addition, there are expanded requirements for post-study arrangements to ensure that participants involved in research are informed of the results and have access to any beneficial treatments that emerge.

The changes agreed are all about providing a greater degree of protection for those involved in research. The revised Helsinki Declaration requires greater transparency in medical research, more accountability and increased patient safety. The changes place further obligations on research sponsors, on researchers themselves and on host governments to protect research subjects.

This is the seventh time the Helsinki Declaration has been revised since its establishment, with notes of clarification being added in 2002 and 2004. It is the most important set of international ethical regulations in biomedical research currently available and is a core document of the WMA. It was first adopted in 1964 and provides the basis for ethical principles governing medical research involving human subjects.


EudraCT: new version launched

European Union — The European Medicines Agency has launched a new version of the European Clinical Trials Database (EudraCT). This new version, EudraCT V9, marks the initial step of a process through which summary clinical trial results will be made publicly available through the EU Clinical Trials Register (EU CTR).

EudraCT is a database used by national authorities to enter protocol-related information on clinical trials submitted by clinical trial sponsors but also includes protocol-related information on clinical trials in third countries if they are included in a Paediatric Investigation Plan (PIP).

EudraCT already contains protocol-related information submitted by sponsors for interventional clinical trials conducted in European Economic Area countries and/or in third countries, when the clinical trial is part of an agreed PIP. As of today, clinical-trial sponsors are encouraged to register on the EudraCT web site to start uploading summary results. Results posted by sponsors in EudraCT will start to become publicly available once the Agency has launched the complementary new version of the EU CTR towards the end of the year. The content and level of detail of the summary results is set out in a European Commission guideline and in its technical guidance.

This initial release of EudraCT will be followed by further updates to the system in 2014 which will provide improved
functionalities for sponsors and EU regulatory authorities. With the launch of these further iterations of EudraCT by mid-2014, the modalities and timing of posting of result-related information as described in the EC guideline will apply, and sponsors will then be required to post result-related information.

The EMA supports international standardization of data requirements for clinical trial registration. The Agency will make the data descriptions and technical specifications available to enable stakeholders to build systems that can generate structured data sets and upload them electronically into EudraCT.

**WHO PQP now charging application fees**

World Health Organization — The WHO Prequalification of Medicines Programme (PQP) has been externally funded until now and was able to operate successfully through the generosity of donor organizations. However, PQP is no longer able to rely solely on this funding.

PQP is not moving toward a full cost recovery model but is looking to achieve a balance between external and internal funding. Over the next few years, WHO will continue to assess this balance and make adjustments as needed. Although this may appear to be a potential disincentive to manufacturers seeking prequalification of their products, fees have been set below those currently being charged by the WHO vaccines and diagnostics prequalification programmes and flexibility has been introduced whereby manufacturers who provide adequate justification may be exempted from fees or charged a reduced fee.

**PQP General Guidelines for Application Fees** provides more information about the fee structure for applications received on or after 1 September 2013 and is available at http://www.who.int/prequal/info_general/documents/guidelines/application_fees/PQP_application_fees_September2013.pdf


**EudraGMDP database: improved information-sharing**

European Union/Japan — The Japanese Ministry of Health, Labour and Welfare (MHLW) and the European Medicines Agency’s Pharmaceuticals and Medical Devices Agency (PMDA) have started entering information on good manufacturing practice (GMP) compliance related to Japanese manufacturers into the EudraGMDP database. This is the first time that information from a non-European regulator has started to be added to EudraGMDP. The initiative is expected to speed up regulatory processes and save time for importers, manufacturers and regulatory authorities.

This development is part of the mutual recognition agreement (MRA) between the European Union (EU) and Japan. It allows the European Medicines Agency (EMA), European national competent authorities and Japanese authorities to use information in EudraGMDP instead of issuing original paper GMP certificates for a number of regulatory procedures, such as marketing-authorization applications or variation applications, including the addition of a new manufacturer. The EU and Japanese regulatory authorities will now accept a reference to a EudraGMDP entry, or a downloadable file or print-out from the database, within the scope of the EU–Japan MRA.
The regulatory procedures concerned by these new measures depend on the legal frameworks in Japan and the EU, and they are clarified in relevant notices from the regulators. The EU and Japanese authorities may still request original paper GMP certificates when GMP compliance information cannot be accessed via EudraGMDP.

The EMA offers ‘read and write’ access to EudraGMDP to the regulatory authorities of all countries with which the EU has an MRA or an agreement on conformity assessment and acceptance of industrial products (ACAA). Most of these countries are already using the information in EudraGMDP for their own regulatory procedures; the Japanese authorities are the first to take the initiative to enter data into EudraGMDP.


Medical device identification system

United States of America — The Food and Drug Administration (FDA) has announced a final rule for the unique device identification system (UDI) that, once implemented, will provide a consistent way to identify medical devices. The UDI system has the potential to improve the quality of information in medical device adverse events reports, which will help the FDA identify product problems more quickly, better target recalls, and improve patient safety.

The UDI system consists of two core items. The first is a unique number assigned by the device manufacturer to the version or model of a device, called a unique device identifier. This identifier will also include production-specific information such as the product lot or batch number, expiration date, and manufacturing date when that information appears on the label.

The second component is a publicly searchable database called the Global Unique Device Identification Database (GUDID) that will serve as a reference catalogue for every device with an identifier. No identifying patient information will be stored in this device information center.

The UDI system will enhance the ability to quickly and efficiently identify marketed devices when recalled, improve the accuracy and specificity of adverse event reports and provide a foundation for a global, secure distribution chain, helping to address counterfeiting and diversion. It will also offer a clear way of documenting device use in electronic health records and clinical information systems. The UDI system is a key component of the National Medical Device PostMarket Surveillance System proposed in September 2012.

In general, high-risk medical devices (Class III) will be required to carry unique device identifiers on their label and packaging within one year and this number and corresponding device information must be submitted to the new database. Manufacturers will have three years to act for most Class II (moderate risk) devices. Manufacturers of Class I devices not exempt from UDI requirements will have five years to act.


Macitentan approved for pulmonary arterial hypertension

United States of America — The Food and Drug Administration (FDA) has approved macitentan (Opsumit®), a new adult treatment for pulmonary arterial hypertension (PAH). Macitentan is an endothelin receptor blocker.

Similar to other members of its drug class, Opsumit® carries a boxed warning...
alerting that the drug should not be used in pregnant women. Female patients can receive the drug only through the Opsumit® Risk Evaluation and Mitigation Strategy (REMS) Programme. This requires that:

- Prescribers should be certified.
- All female patients should be enrolled and comply with applicable pregnancy testing and contraception requirements before initiating treatment.
- Pharmacies should be certified to dispense Opsumit®.

Common side effects observed include anaemia, nasopharyngitis, sore throat, bronchitis, headache, flu and urinary tract infection.


**Liposorber Apheresis System® approved for paediatric glomerulosclerosis**

**United States of America** — The Food and Drug Administration (FDA) has approved Liposorber LA-15 System® to treat paediatric patients with primary focal segmental glomerulosclerosis (FSGS) either before transplant, or after renal transplantation in which there is recurrence of FSGS.

FSGS is a chronic kidneys disease which causes excessive loss of protein from the blood into the urine leading to nephrotic syndrome and kidney failure. A majority of children with primary FSGS will progress to end stage renal disease and will require either kidney dialysis or kidney transplant. About one quarter to one half of FSGS patients that receive a kidney transplant will have a recurrence of FSGS in their transplanted kidney.

The Liposorber LA-15 System®, a blood processing system that is used outside the body, includes disposable components and a control/monitor unit. The device works by removing certain lipoproteins from the patient’s blood. The Liposorber LA-15 System® was first approved in the United States in 1996 for lowering low density lipoprotein cholesterol in certain patients with familial hypercholesterolemia (FH).


**Riociguat approved for pulmonary hypertension**

**United States of America** — The Food and Drug Administration (FDA) has approved riociguat (Adempas®) for adult treatment of two forms of pulmonary hypertension.

Riociguat is a soluble guanylate cyclase stimulator intended for patients with chronic thromboembolic pulmonary hypertension (CTEPH) after surgery or patients who cannot undergo surgery, to improve their ability to exercise. Riociguat is also indicated for patients with pulmonary arterial hypertension (PAH) to improve their ability to exercise and to delay clinical worsening of their condition.

Adempas® carries a boxed warning alerting patients and healthcare professionals that the drug should not be used in pregnant women. Female patients can receive the drug only through the Adempas® Risk Evaluation and Mitigation Strategy (REMS) Programme. This requires that:

- Prescribers should be certified.
- All female patients should be enrolled and comply with applicable pregnancy testing and contraception requirements before initiating treatment.
- Pharmacies should be certified to dispense Adempas®.
Common side effects observed in patients treated with riociguat included headache, dizziness, dyspepsia, peripheral edema, nausea, diarrhoea and vomiting.


Vortioxetine approved for major depressive disorder

United States of America — The Food and Drug Administration (FDA) has approved vortioxetine (Brintellix®) to treat adults with major depressive disorder.

The most common side effects reported by participants taking vortioxetine in clinical trials included nausea, constipation and vomiting. Brintellix® and other antidepressant drugs have a boxed warning and a medication guide alerting patients and healthcare professionals that antidepressants can increase the risk of suicidal thoughts and behavior in children, adolescents and young adults ages 18 to 24 during initial treatment.

Reference: FDA News Release, 30 September 2013 at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements

Pertuzumab approved as neoadjuvant breast cancer treatment

United States of America — The Food and Drug Administration (FDA) has granted accelerated approval to pertuzumab (Perjeta®) as part of a complete treatment regimen for patients with early stage breast cancer before surgery (neo-adjuvant setting). Perjeta® was approved in 2012 for the treatment of patients with advanced or metastatic HER2-positive breast cancer.

Perjeta’s new use is intended for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer who are at high risk of having their cancer return or metastasize, or of dying from the disease. It is to be used in combination with trastuzumab and other chemotherapy prior to surgery and may be followed by chemotherapy after surgery. Following surgery, patients should continue to receive trastuzumab to complete one year of treatment.

The confirmatory trial for this accelerated approval is being conducted in participants with HER2-positive breast cancer who had prior breast cancer surgery and are at high risk of having their cancer return. More than 4800 participants are enrolled in this trial, which will provide further data on efficacy, safety and long-term outcomes. Results are expected in 2016.

The most common side effects reported in participants receiving pertuzumab plus trastuzumab and docetaxel were hair loss, diarrhoea, nausea and a decrease in white blood cells. Other significant side effects included decreased cardiac function, infusion-related reactions, hypersensitivity reactions and anaphylaxis.


Paclitaxel: expanded use for late-stage pancreatic cancer

United States of America — The Food and Drug Administration (FDA) has expanded the approved uses of paclitaxel protein-bound particles for injectable suspension, albumin-bound (Abraxane®), to treat patients with metastatic pancreatic cancer.

Abraxane® is intended for use with gemcitabine in patients with pancreatic cancer that has spread to other parts of the body.

Common side effects observed in Abraxane® plus gemcitabine treated participants include neutropaenia,
thrombocytopaenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhoea, pyrexia, vomiting, rash and dehydration. The most common serious side effects were pyrexia, dehydration, pneumonia and vomiting. Other clinically important serious side effects included sepsis and pneumonitis.

Paclitaxel was also approved to treat breast cancer in 2005 and non-small cell lung cancer in 2012.


Ibrutinib approved for mantle cell lymphoma

United States of America — The Food and Drug Administration (FDA) has approved ibrutinib (Imbruvica®) to treat patients with mantle cell lymphoma (MCL), a rare and aggressive type of blood cancer.

MCL is a rare form of non-Hodgkin lymphoma and represents about six percent of all non-Hodgkin lymphoma cases in the United States. By the time MCL is diagnosed, it usually has already spread to the lymph nodes, bone marrow and other organs.

Ibrutinib is intended for patients with MCL who have received at least one prior therapy. It works by inhibiting the enzyme needed by the cancer to multiply and spread. Imbruvica® is the third drug approved to treat MCL. Velcade® (2006) and Revlimid® (2013) are also approved to treat the disease.

The most common side effects reported in participants receiving ibrutinib are thrombocytopenia, diarrhoea, neutropenia, anemia, fatigue, musculoskeletal pain, edema, upper respiratory infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting, and decreased appetite. Other clinically significant side-effects include bleeding, infections, kidney problems and the development of other types of cancers.

Eslicarbazepine acetate approved for adult seizures

United States of America — The Food and Drug Administration (FDA) has approved eslicarbazepine acetate (Aptiom®) as an add-on medication to treat seizures associated with epilepsy.

Eslicarbazepine acetate is approved for the treatment of partial seizures, the most common type of seizure seen in people with epilepsy.

The most common side effects reported by patients receiving eslicarbazepine acetate in clinical trials included dizziness, drowsiness, nausea, headache, double-vision, vomiting, fatigue and loss of coordination. These and other side effects and recommendations for monitoring are described in the drug label.

Like other antiepileptic drugs, eslicarbazepine acetate may cause suicidal thoughts or actions in a very small number of people.


Dolutegravir approved for HIV

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended granting a marketing authorization for dolutegravir (Tivicay®) in combination with other antiretroviral medicines for the treatment of adults and adolescents over twelve years of age infected with human immunodeficiency virus (HIV).

Dolutegravir can be used in adult patients with and without resistance to the integrase class and in adolescents infected with HIV-1 without resistance to the integrase class.

Dolutegravir has demonstrated its efficacy in large scale studies covering previously untreated patients as well as patients with advanced treatment histories and resistant to multiple classes of HIV medicines. It also demonstrated a high barrier to resistance.

Dolutegravir has been recommended for marketing approval together with a risk management plan (RMP) which covers the risk of infrequent but potentially severe hypersensitivity reactions.

The EMA is currently consulting on new draft guidance for development of these medicines, taking into account changes in the therapeutic landscape.


Delamanid and para-aminosalicylic acid approved for multidrug-resistant tuberculosis

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended the authorization of delamanid (Deltyba®) and para-aminosalicylic acid (Paraaminosalicylic acid Lucane®), two treatment options for use in combination with other medicines against multidrug-resistant tuberculosis.

Multidrug-resistant tuberculosis is defined as tuberculosis caused by Mycobacterium tuberculosis that is resistant to at least isoniazid and rifampicin, which are two antituberculosis medicines used in standard treatment. Approximately 450 000 cases of multidrug-resistant tuberculosis occur globally every year, which corresponds to approximately 5% of the world’s annual burden of tuberculosis. In the European Union, tuberculosis is an orphan indication. It was estimated in 2011 to occur in 2.3 out of 10 000 people.
Deltbyba®: The CHMP recommended granting a conditional marketing authorization for Deltbyba® (delamanid), for the treatment of adult patients with pulmonary infections due to multidrug-resistant tuberculosis when an effective treatment regimen cannot otherwise be devised for reasons of resistance or tolerability. Additional studies on the long-term effectiveness of Deltbyba® need to be conducted.

Para-aminosalicylic acid Lucane®: The Committee also recommended granting a marketing authorization for Para-aminosalicylic acid Lucane® against multidrug-resistant tuberculosis in adults and paediatric patients when an effective treatment regimen cannot otherwise be devised for reasons of resistance or tolerability.

Para-aminosalicylic acid, of which Para-aminosalicylic acid Lucane® is a new formulation, was the second medicine to be introduced for the treatment of tuberculosis, in 1946, and was part of standard-of-care treatment until the 1970s. Its use resumed in the 1990s with the emergence of multidrug-resistant tuberculosis.


Sofosbuvir approved for chronic hepatitis C

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human use (CHMP) has recommended granting a marketing authorization for sofosbuvir (Sovaldi®) for use in combination with other medicinal products for the treatment of chronic hepatitis C (HCV) in adults.

Sofosbuvir is the first representative of a new class of antivirals that act as inhibitors of an essential enzyme of HCV, the NS5B ribonucleic acid polymerase. This medicine provides the first interferon-free treatment option for chronic hepatitis C.

Furthermore, when sofosbuvir is used in combination with pegylated interferon as well as ribavirin, shortened treatment duration down to 12 weeks (compared to 24–48 weeks with the current standard of care) is possible and provides high efficacy. This is of value considering the side-effect profile of interferon.

HCV infection is the most common single cause of liver transplantation in the EU. However, patients who do undergo liver transplantation due to hepatitis C have a worse prognosis than patients who do so for other reasons because recurrence of the virus in the graft is near-universal and often aggressive. For many of these patients, there are currently no approved treatment options that are likely to be effective.

In clinical trials, Sovaldi® in combination with ribavirin has shown its capacity to prevent reinfection of the graft, and thus provides a treatment option for patients with HCV infection who are on the waiting list for liver transplantation.