



Current topics

Moderator: Professor Alfred Hildebrandt, Germany

Quality issues

“For export only” manufactured drugs and cosmetics that are not legally used in country of manufacture

Dr Adeline Osakwe, Nigeria

There are a variety of pharmaceutical products and cosmetics that are not registered in the country where they are manufactured. These products contain ingredients that are either banned or not considered fit for use in the country of manufacture. However, they are allowed to be manufactured for export. Regulatory bodies should ensure that products that are not fit to be used in their own countries should not be manufactured for export.

WHO Certification Scheme: input for implementation

Dr Maura Linda Sitanggang, Indonesia

The WHO Certificate of Pharmaceutical Product (CPP) is a document that gives information on the safety and efficacy of a pharmaceutical product. However, for some products, safety labelling and indicated use may differ from one country to another. For example, marketing authorization for sibutramine has been suspended in some countries because of reported cardiovascular side-effects, although it is still under review with inconclusive results in other countries. Meanwhile, industry claims that the drug is safe for pathological obesity as long as it is not used as a slimming pill. Similarly, the awareness of relative risk with the use of synthetic or natural-based hormonal compounds in hormone replacement therapy is different in different countries. It is difficult for the WHO CPP scheme address the differing safety aspects of such cases.

Regarding efficacy, for rofecoxib, there are different indications stated in CPP from different countries, such as osteoarthritis in some countries and

osteoarthritis and acute pain in others. As the CPP is an instrument within the WHO Certification Scheme used when a product is under consideration for a product licence in a country, it would be useful if the certification process could provide guidance and clarification on the safety, efficacy, and quality of pharmaceutical products entering different countries.

Value of joining the Pharmaceutical Inspection Cooperation Scheme (PIC/S) for developing countries: the Malaysian experience

Mr Mohammed Zin Che Awang, Malaysia

The PIC/S was implemented in 1995. Its objectives are to facilitate networking and confidence-building, to promote the quality of inspections and quality assurance of inspectorates, to coordinate training of inspectors, to provide a framework for the exchange of information and experience in GMP, and to enhance global harmonization of GMP.

Malaysia applied to join the PIC/S in February 2000. After assessment of the Malaysian documents on the regulatory system, an assessment visit by a PIC/S team was made in March 2001 and a reassessment visit in November 2001. Malaysia was accepted as the 26th member in January 2002.

There is a need to harmonize GMP inspection standards through the training of inspectors in developing countries to ascertain the quality of starting materials and manufactured pharmaceutical products and the PIC/s provides a platform for activities in this area.

Pharmacopoeial specifications for new drug entities

Dr Ashwini Kumar, India

The availability of harmonized quality specifications of drugs through pharmacopoeias is central to all drug regulatory authorities for the access to safe, efficacious and quality medicines. There are some new drugs that are internationally traded and included in the WHO Essential Drugs Lists, but for which there are no readily available pharmacopoeial specifications.

A meeting was arranged during the 10th ICDRA, with participants from Brazil, China, Czech Republic, India, Russian Federation, Thailand and Zimbabwe, and telephone links to the European Pharmacopoeia and the United States Pharmacopoeia, to discuss the development of pharmaceutical specifications for new drug entities. Efforts are needed to encourage international harmonization in the development of

common specifications and international reference standards, with a special focus on new drug entities and drugs with major health impact, and the development of screening tests to help combat counterfeit drugs. It was agreed that the topic of pharmacopoeial requirements should be proposed for inclusion in the next ICDRA.

Role of drug regulatory authorities

Improving the impact of drug regulatory authorities on public health

Dr John Lisman, Netherlands

There are actually two worlds in the area of pharmaceutical products. The real world of prescribers and patients: medicines are prescribed for, and used by, patients, who may then have side-effects or adverse reactions, and may be cured. The other world is that of the drug regulatory authorities and the pharmaceutical industry. For maximum effectiveness in public health terms, communication between the two worlds is important.

In today's situation, there is little or no connection between the two worlds. Many pharmaceutical products are used "off-label" and some prescription drugs are used as over-the-counter products. In order to promote the rational use of medicinal products, crossing the border between these two worlds could have a positive impact on public health. Drug regulatory authorities should be more transparent and proactive in the dissemination of relevant drug information to the public, which will improve rational drug use and protection of public health.

Strengthening drug regulatory authorities in small Pacific Island nations

Mr Peter Zinck, Fiji

The South Pacific Islands comprise 14 countries, including Australia, New Zealand, Papua New Guinea, Samoa, Tonga, Solomon Islands and Fiji. The total population is around 26 million, of whom 20 million are in Australia and New Zealand and 4 million in Papua New Guinea. The remaining 2 million are divided among the other 11 countries.

The regulatory authorities of these small import-oriented countries face many challenges, particularly where gross domestic product is low. Drug budgets are limited, purchasing power is small and it is

difficult to source products that are of good quality, reliable and from credible suppliers. Furthermore, because human resources are limited, administrative processes and systems, technical capacity and quality control measures are generally inadequate.

Because of these limitations, DRAs in small Pacific Island nations are exploring the opportunities for regional collaboration in the areas of sharing relevant regulatory information, drug registration, pharmacovigilance and GMP inspection in the hope of strengthening their regulatory capacity. Like New Zealand, which has a strategic alliance with Australia, the small Pacific Island nations are looking for potential twinning arrangements with key regulatory authorities in the region.

Transparency of data

Dr Batya Haran, Israel

One of the key attributes of organizations and agencies today, in particular in the public health arena, is transparency. There are three aspects to transparency, namely (1) public health; (2) patient's rights, and (3) building confidence in the regulatory authority. We have to provide reliable information to patients and physicians and, when a product needs to be recalled, we should avoid creating unnecessary panic among the public.

In general, the more information one can give the better. However, when considering what kind and how much information to release, three aspects should be taken into account: (1) the confidentiality of the data that belong to the manufacturers; (2) the confidentiality of the data that belong to the patients; and (3) the need for transparency from the regulatory authorities. In summary, all regulatory authorities have to enhance transparency, providing information that is balanced and reliable.

Miscellaneous topics

Kava

Dr Rolf Spang, Switzerland

Four cases of severe hepatic complications associated with a kava root acetone extract occurred within a period of 7 months in Switzerland up to spring 2000. The incidence of severe hepatic

complications can be estimated at around 1 in 35 000 patient-months in Switzerland and 1 in 175 000 patient-months globally.

Taking into account the benefits and available alternatives, the registration of the kava root acetone extract in Switzerland was provisionally suspended in September 2000 and definitely withdrawn in April 2001. The alcohol extract and a synthetic preparation containing 1-kavaine, with a seemingly lower incidence of severe liver reactions, have remained on the market, but were moved in autumn 2001 to “pharmacy only” status with a strong warning on the risk of liver injury and possible early symptoms.

While Switzerland is still receiving reports of severe liver reactions associated with the acetone extract, one recent case of hepatocellular injury has been attributed to a combination of the synthetic kavapyrone 1-kavaine combined with magnesium orotate and vitis viniferae extractum. In the meantime, several reports of severe hepatitis or liver injury associated with ethanol kava extract have been notified in other countries, most of them in Germany.

Kava extracts are not regulated as drugs in many countries. France, the United Kingdom and the United States have all taken different actions in the control of kava extract. Switzerland will decide on further action with respect to the ethanolic extract after examining the new international data.

Xenotransplantation and xenotourism: time for concerted regulatory action

Dr Stewart Jessamine, New Zealand

Xenotransplantation is the transplantation of living cells, tissues, or organs between species, while allotransplantation is the transplantation of cells or organs within species. Xenotransplantation is a new technology and there are many factors to be considered, such as physiology, immunology, microbiology and ethical issues.

In terms of public health implications, all xenografts contain endogenous retroviruses which can infect cultures of human cells. However, whether these endogenous retroviruses can infect human cells in vivo or can replicate in human cells, thus causing disease, is still unknown. WHO and several regulators have urged that xenotransplantation be treated with extreme caution as the consequences of any emergent new infection could be serious.

Since xenotransplantation is unlike other medical treatments, the standard approaches to regulation, informed consent and ethical review may be inadequate. WHO urges each regulator to make its own risk-benefit assessment of the associated ethical and cultural issues.

In New Zealand, the Gene Technology Advisory Committee and the Royal Commission on Genetic Modification have recommended that xenotransplantation should not proceed in New Zealand until extensive public consultation has occurred. The Medicines Act was amended to place a temporary control over three “restricted biotechnical procedures”, namely xenotransplantation, cloning and genetic modification of human embryos. A comprehensive new regulatory regimen will be developed in the next four years.

New Zealand has declined an application to conduct xenotransplantation; the applicant has since approached several nearby countries with less strict regulatory systems and offered incentives to these countries to allow patients from New Zealand to be flown there for treatment. This could be called xenotourism. However, all attempts were rejected by the governments of these countries. The international consensus is that it is ethically unacceptable for a country to allow xenotransplantation to proceed within its borders without regulatory oversight and control.

Recommendations

1. There should be only one standard of quality, safety and efficacy of medicines, whether these are produced for local consumption or for export only. Member States should regulate drugs for export in accordance with appropriate international standards.
2. WHO should collaborate closely with the PIC/S to enhance capacity building of national inspectorates. This could be undertaken within the concept of a Global Alliance for Quality of Medicines.
3. WHO should continue its efforts towards the development of international specifications and pharmacopoeial requirements and the establishment of international reference standards for drugs responding to major public health needs.
4. In collaboration with Member States, WHO should develop guidelines for the regulation of xenotransplantation.