WHO Drug Information

Contents

WHO Drug Information

is now available at:

http://www.who.int/druginformation

Regulatory Challenges

Drug regulatory authorities recommend action

The Eleventh International Conference of Drug Regulatory Authorities (ICDRA) took place in Madrid, Spain from 16 to 19 February 2004. The ICDRA was hosted by the Ministry of Health of Spain and the Spanish Agency for Medicines and Health Products in collaboration with the World Health Organization (WHO). The Conference was opened by the Minister of Health of Spain, and the Director-General of WHO. Over 240 participants from drug regulatory authorities in 113 countries were present.

Drug regulatory authorities are continually challenged by the rapid development and sophistication of medicinal products, new technologies and health care techniques. Such developments pose a heavy demand on regulatory control systems which are often unable to respond due to inadequate resources. Together with enlargement of distribution and access channels, growing use of the Internet and penetration of substandard and counterfeit medicines into many markets, the regulator's task is becoming more and more daunting. One objective of the ICDRA is to give regulators the opportunity to exchange information, leverage collaboration and strengthen vital links with other agencies experiencing similar problems.

During the conference, the four-day programme focused on presentation and discussion of many important topics that have an impact on public health. A progress report on implementation of recommendations from the Tenth ICDRA held in Hong Kong in 2002 was introduced by Hong Kong SAR China and presented by WHO. Participants appreciated progress made in many areas of medicines regulation since the Tenth ICDRA in Hong Kong in 2002. As globalization continues and has a profound impact on the development and marketing of medicines, the need for strong international collaboration between regulatory authorities together with government commitment to strengthening regulatory systems and policies, and mechanisms to intensify international collaboration were highlighted as the most effective means to safeguard public health. (http://www.who.int/medicines/organization/qsm/activities/drugregul/icdra.shtml)

The ICDRA continues to be an important forum for WHO and drug regulatory authorities to meet and discuss actual problems and latest developments in medicines regulation with the main objective of improving safety, efficacy, quality and access of medicines. The ICDRA continues to support collaborative initiatives with a focus on harmonization of medicines control. The Twelfth ICDRA will be held in the Republic of Korea in 2006

Recommendations

Recommendations from the Eleventh ICDRA will form a basis for future collaboration among Member States, drug regulatory authorities, WHO, interested agencies and institutions, and set priorities for WHO action and support.

Regulatory aspects of access to medicines

The mission of regulatory authorities is to promote and protect public health. The lack of access to medicines remains a huge concern, whether these are essential medicines, vaccines, orphan drugs or drugs for tropical diseases. To facilitate access, regulators and all other stakeholders need to be actively involved in identifying difficulties and seeking solutions leading to balanced approaches to access which do not compromise public health safeguards.

Recommendations

- Regulators have a role and responsibility to facilitate access to drugs of public health importance including proposing changes to the respective regulations in order to facilitate access without compromising quality, safety and efficacy.

- When considering marketing authorization (registration) applications, regulators should give priority to medicines of high public health importance in their countries. Regulators should consider mechanisms to facilitate registration, such as reducing fees or other related costs.

- As part of the medicines approval process, regulators should carry out an appropriate risk benefit assessment to allow for adjustment to the needs and profile of the anticipated patient populations.

Strengthening of regulatory frameworks for medicinal products

The establishment of a well-functioning national regulatory system as an integral component of effective public health leads to better patient protection through provision of medicines which are safe, efficacious and of good quality. Cooperation, communication and trust between national regulatory authorities based on common principles and harmonized approaches will strengthen the effectiveness of national regulation and international collaboration. Transparency is an important aspect of regulatory systems and helps to build public confidence, while facilitating cooperation and information exchange among regulators.

- Member States should strengthen their efforts to increase transparency of the work of national regulatory authorities. Regulatory guidelines, procedures and criteria as well as data about registered medicines should be made publicly available to all stakeholders.

- National regulatory authorities should make available to the public, in understandable language, negative and positive assessment reports (including pharmacovigilance reports).

- National regulatory authorities should provide applicants for a marketing authorization with full information on regulatory decisions and an explanation of the reason for such decisions.

Pharmacovigilance Practices

Spontaneous reporting is the mechanism used for compiling adverse drug reaction reports and regulatory authorities take important decisions based on these data. Pharmacovigilance is a broad concept, and also includes the re-evaluation of marketed drugs, risk management, communicating drug information, promoting rational drug use and crisis preparedness. It is becoming increasingly important to provide training in all of these activity areas and to carry out intensive monitoring of new drugs in order to evaluate the risk/benefit. Increasingly, medicines are being donated for off-label indications for specific public health needs and it is important that sufficient data is available to the national regulatory authority on safety, efficacy and quality.

Recommendations

- Member States should be encouraged to involve pharmacovigilance staff in public health risk assessment, management and communication for medicines safety activities including adverse reactions monitoring, medicines re-evaluation, drug information, rational drug use, lack of efficacy and crisis preparedness.

- Increasingly, certain medicines are approved based on special conditions, such as finalization and reporting of Phase IV studies. National regulatory authorities should collaborate on harmonizing the terms of conditional approval, and develop systems to allow sharing of information on medicines in this category.

- All sponsors and donors of medicines should provide sufficient data to allow the national drug regulatory authority to be assured that the product being donated, or recommended for use, meets appropriate standards of safety, quality and efficacy. Obligations to conduct post-marketing surveillance as a public health protection measure should also lie with sponsors and donors, as appropriate. International agencies and aid programmes should make every effort to comply with these requirements and provide the necessary data.

- Member States should be encouraged to establish databases of clinical information suitable for epidemiological studies to examine and quantify signals of possible emerging risk.

- WHO should coordinate and develop training resources in pharmacovigilance and pharmacoepidemiology and expand its commitment to include training programmes in each of its regions.

- WHO should provide, upon request, technical advice and support to Member States on the appropriateness of post-marketing surveillance plans submitted by sponsors when a medicine is being introduced to manage a specific public health campaign in that country.

• WHO should investigate the feasibility and potential utility of creating a database of "recommendations for action" arising from evaluations made by national regulatory authorities of the periodic safety update reports (PSURs) in order to improve the usefulness of such information by making this generally available.

Pharmacopoeias in a changing regulatory environment

Pharmacopoeial standard-setting for starting materials and finished dosage forms underpins the work of drug regulatory authorities by providing the means of ensuring the quality of medicines, particularly multisource (generic) products.

Increased collaboration and coordination at international level of pharmacopoeial bodies and all related parties is needed: (i) for the development and analysis of quality control specifications; (ii) to speed up development of pharmacopoeial specifications; (iii) to address the increasing diversity and complexity of impurity profiles and limits set at international level, especially for pharmaceutical starting materials; and (iv) to promote independent and worldwide validation of analytical methods to ensure the quality of traded and sourced products internationally.

The promotion of good quality pharmaceutical products, and the development of quality control methods - in particular to detect counterfeit drugs - is important for public health. Participants agreed on the need for international harmonization of quality control specifications, and recognized WHO's leadership role in providing normative guidance for quality control and quality assurance of medicines, particularly in the development and international harmonization of pharmacopoeial specifications for new drug entities, including antiretrovirals, anti-tuberculosis and antimalarial medicines.

Recommendations

• Member States should encourage close collaboration between regulatory authorities and pharmacopoeial secretariats/commissions.

• In collaboration with those concerned, WHO should organize an international conference on pharmacopoeial issues to exchange views and experiences among pharmacopoeial bodies and regulators.

• In collaboration with parties concerned, WHO should develop a harmonized approach to providing internationally validated specifications for medicines for neglected and emerging diseases of high public health risk.

• WHO should continue to support the establishment of international chemical reference substances (ICRS) and assist in their supply, particularly for medicines used in the treatment of diseases of high public health impact.

Regulatory assessment of combination products

Combination products for various diseases have always been used in medical practice. Today, HIV/AIDS, tuberculosis and malaria are the major infectious diseases threatening public health and the focus of many national, regional and global initiatives. Combination therapy is considered essential for their treatment as well as for the prevention of drug resistance. Attempts to manage these diseases include the development of fixed dose combinations (FDC) of individual drugs to be administered together in one finished dosage form. Well documented clinical evidence of the efficacy and safety of the loose combination is a key entry point for development of any FDC drug. Currently, there are no uniform principles, guidelines or international standards addressing the development and regulatory assessment of FDCs. Only a few countries have specific FDC regulatory guidelines available and irrational combinations are still common in several markets.

Recommendations

• In countries where specific guidelines do not exist regulators need to establish clear quality, safety and efficacy requirements for registering fixed dose combination medicines, particularly prescription-only drugs. Regulators should critically review the existing fixed dose combination drugs on the market and withdraw those which do not meet these requirements.

• WHO is urged to create — as a matter of urgency — model guidelines for regulatory approval of prescription-only fixed dose combination drugs with special emphasis on drugs for communicable diseases with high public health impact.

Regulators, good clinical practice and ethics

Application of good clinical practice (GCP) guidelines assures that clinical studies on medicinal products meet scientific and ethical requirements. However, recent advances in medicine may encompass areas of clinical research not covered by existing GCP guidelines and this gap

should be filled since all clinical research, including research on gene therapy and biotechnology products, should be conducted under rigorously implemented GCP. Since data on the safety and efficacy of innovative products may be limited, it is important that national regulatory authorities strengthen mechanisms to share knowledge and experience. Given the increasing tendency to involve vulnerable subjects in research, there is a special need to strengthen the application of ethical principles in research carried out in these populations.

Recommendations

- Member States should implement good clinical practice (GCP) guidelines to assure that clinical studies follow scientific and ethical requirements. All clinical research, not only for medicinal products, needs to be regulated.
- Member States should ensure that informed consent processes, particularly for vulnerable populations and for obtaining biological samples for genetic studies, meet all GCP, national and ethical requirements.
- Member States should recognize that gene therapy is a new complex area of medicine needing rigorously implemented GCP and ethical oversight.
- WHO is requested to gather existing knowledge and experience of safety, efficacy and quality of innovative biotechnology products and share this information with Member States.
- WHO is requested to accelerate its work in regulatory capacity building for assessment of vaccines and medicines of public health importance and to explore options for providing external regulatory expert support for assessment of clinical trial applications in countries with limited resources.

Public health needs vs. the marketplace

Development of new drugs is often driven by market forces. Some medicines for priority disease of public health impact are commercially unattractive, and this is often because they are unaffordable by poor populations. Effective mechanisms compensating for this market failure are needed to bridge the gap. Regulators, together with other stakeholders, can play an important role in supporting initiatives aimed at creating new drugs for diseases where there is no market attractiveness by motivating investment into research and development. However, there is also a regulatory capacity gap to overcome, as regulators from developing countries have limited capacity to advise on drug development or assess the safety, efficacy and quality of new drugs created for diseases exclusively prevalent in those settings.

Recommendations

- WHO is encouraged to continue cooperation with Member States, industry and other stakeholders in order to promote and facilitate development of new treatments for diseases that have little market potential, in particular for diseases prevalent in developing countries (neglected diseases). Mechanisms and incentives should be created for more proactive involvement of national regulatory authorities in all stages of research and development of these products.
- WHO should continue facilitating regulatory capacity building and networking among regulators of different countries in order to empower regulators in countries with limited resources to take informed and evidence-based decisions.
- WHO should explore the potential of creating distance learning courses for regulators.

Safety of herbal medicines

The use of herbal medicines is increasing rapidly worldwide. Although the reasons for this may vary in different settings, the safety of herbal medicines is a common global concern. Both public and national health authorities are committed to making progress in ensuring the safe use of herbal medicines. This is a very complicated and complex issue because of differing regulatory requirements, availability and suitability of technical methods for quality control, post-marketing quality surveillance, and safety monitoring, the presence or absence of qualified practitioners and consumer education. Major issues concerning the safe use of herbal medicines are set out below.

Recommendations

- The safe use of herbal medicines requires adequate regulation. Member States should continue to adapt their national and/or regional regulatory framework, including pharmacovigilance, to the specific requirements of herbal medicines. WHO should continue to provide support including guidance and training programmes.

- Quality assurance and quality control of herbal medicines presents specific challenges. WHO should continue to provide technical guidelines, particularly for the quality control of combination products and criteria for reference substances and materials.
- Awareness amongst consumers on the benefits and limitations of herbal medicines needs to be strengthened. Member States should consider preparing a policy on consumer information and guidelines on the advertising of herbal medicines. WHO should provide general guidance to support these activities.
- Providers of traditional/complementary health care play an important role in the safe use of herbal medicines. Member States should explore appropriate mechanisms to ensure adequate training and education of these health care providers. WHO should provide policy and technical guidance.
- Regulatory agencies should work together to make the best use of scientific resources related to herbal medicines. Sharing national experience and information is crucial. WHO should facilitate these activities e.g. by providing updated monographs on medicinal plants and technical/regulatory guidance.

Assuring quality and safety of blood products

Blood and blood products are essential for the treatment of a number of life-threatening conditions. However, because blood may transmit infectious agents this can also cause severe harm to the recipients. During the Ninth and Tenth ICDRAs, emphasis was therefore given to procedures aimed at inactivating and removing infectious agents. In order to avoid transmission of infectious agents in a reliable manner, good manufacturing practice (GMP) has to be implemented as an essential tool of quality assurance. In addition, adherence to GMP at all levels of the process, from donor to recipient, is a prerequisite for consistent quality in the preparation of blood and blood products.

Recommendations

- WHO's policy to give high priority to the implementation of GMP in blood and plasma collection establishments is welcomed. Educational programmes and training opportunities should be continued and strengthened. Guidance documents should be developed and/or updated.
- In order to facilitate the enforcement of GMP in both blood/plasma collection and fractionation facilities, WHO should promote joint inspections between several countries under the guidance of experienced inspectors.
- WHO should promote cooperation between regulatory authorities with regard to GMP compliance aimed at mutual agreements among Member States.
- WHO should contribute to advancing the technical expertise of regulatory authorities by enabling the creation of regional networks to facilitate their regulatory role in the area of blood and blood products.
- WHO should facilitate the formation of a global network of regulatory authorities for blood and blood products.

Human tissue: problems and challenges for regulators

The transplantation of human cells, tissues and organs has become the treatment of choice for a wide range of both fatal and non-fatal diseases. The volume and complexity of activities relating to transplantation is growing rapidly. The ethical and safety risks of transplantation require effective regulatory oversight at national level, and international cooperation.

Given the rapid global increase in the allogenic transplantation of cells, tissues and organs, and the associated ethical and safety risks this entails, Member States should develop and implement effective national regulation of procurement, processing and transplantation of human cells, tissues and organs.

Recommendations

- To facilitate this process, WHO is requested to develop clear guidelines for the quality, safety and efficacy of human cell, tissue and organ transplantation.
- To complement the regulation of human cell, tissue and organ transplantation, Member States should develop and implement effective surveillance after cell, tissue and organ transplantation.
- WHO should facilitate these surveillance activities by development of appropriate written standards and reference materials

Regulatory tools for providing drug information

Accurate drug information is essential for the rational use of medicines. Assessment of safety, efficacy and quality of products includes also assessment of product information provided by the applicant of the marketing authorization. Although national regulatory authorities have the responsibility of validating the correctness and appropriateness of the product information, resource constraints may limit the capacity of small regulatory authorities to be able to verify the quality of information provided by the manufacturers.

Recommendations

- National regulatory authorities should establish and implement requirements for product information in line with the information provided in the summary of product characteristics (SPC) as part of their national drug registration process.

- At national level, product information should be harmonized for all products having the same active ingredient.

- WHO should develop guidance and new tools to control promotion and drug information.

- National regulatory authority-approved information should be the reference for providing independent information and the benchmark for controlling promotion. Approved information should be made available on the regulatory agency website.

Harmonization updates

Harmonization of technical requirements for the registration of medicines can contribute to public health by improving access to safe, effective and good quality medicines. It can also facilitate development of a fair and transparent regulatory process, improve international collaboration, reduce duplication of work by different regulatory agencies and facilitate trade and competition. Harmonization initiatives are ongoing in all WHO regions. The major focus of many of those initiatives is to first harmonize basic regulatory requirements for generic drugs. In contrast, the International Conference of Harmonization (ICH), an initiative set up between the European Union, Japan and USA, has been focusing on requirements to evaluate the quality, safety and efficacy of new innovative drugs, thus avoiding the necessity to duplicate many time-consuming and expensive test procedures. ICH has established a Global Cooperation Group for non-ICH harmonization initiatives to learn from ICH experience.

Recommendations

- WHO should continue to support regional and sub-regional harmonization initiatives that contribute to public health priorities. WHO should facilitate information exchange between different harmonization initiatives and report on progress made in these initiatives through its website.

- Regional harmonization initiatives should have clear public health priorities according to local needs, clear milestones to measure progress, and appropriate resources to make progress possible. Member states are encouraged to facilitate harmonization which will increase availability and accessibility of medicines.

- The ICH Global Cooperation Group should continue to serve as a forum of discussion and dialogue between ICH and non-ICH harmonization initiatives recognizing different regional needs, priorities and capacity.

Promoting good regulatory practices

To meet the objectives of promoting and protecting public health, national regulatory authorities need to carry out their functions effectively and efficiently within a set of principles based on transparency and good governance. The issues that are necessary to promote good regulatory practices nationally and internationally include sustainability of resources, optimal structure, effective cooperation within the agency and with other agencies, transparency and accountability, competence in evaluating efficacy, safety, and quality, timeliness, independence, collaboration as a service provider, sharing information, harmonization, and mutual recognition. In many cases, regulatory authorities do not have sufficient resources to carry out these activities. Most importantly, regulatory agencies must be accountable and decision-making processes must be transparent but this needs to be balanced against the need for protecting the confidentiality of the data that has been submitted by the manufacturer. Sources of information and the decision process should be made publicly available whenever possible.

Good regulatory practices thus cover an evolutionary process, with good practices built into the systems which continuously reinforce collaboration and trust. Regulatory authorities should

establish mechanisms to ensure the quality of the procedures they operate to.

Recommendations

- WHO should develop the tools and guidelines needed to help national regulatory authorities effectively implement the principles of good regulatory practices.
- Member States should encourage interagency cooperation for effective implementation of drug regulation involving national regulatory authorities, customs, judiciary, police, civil society and other relevant bodies set up to protect public health.
- National regulatory authorities should formulate a clear mission statement to reinforce effective and efficient drug regulation and customer satisfaction and make use of benchmarking to improve their performance.
- National regulatory authorities should nurture good regulatory governance (integrity, transparency, accountability, public service ethics) to establish credibility and gain confidence. The political governance responsible for national regulatory authorities should promote teamwork, overcome bureaucracy and streamline work.
- WHO should promote and provide technical assistance for the evaluation of regulatory capacity of national regulatory authorities in order to analyse the situation and to undertake necessary corrective measures.

Regulatory aspects of supply of quality medicines

Access to quality medicines contributes to improving human health and promoting wellbeing. Rigorous implementation of good manufacturing practices in the production of medicines will ensure that only safe, quality products are allowed on the market.

The importance of quality has been repeatedly underlined by the occurrence in various countries of counterfeit and substandard drugs. Evidence shows an increase in production, distribution and sale worldwide of counterfeit, spurious and substandard medicines which do not comply with any quality standards. Such products are a waste of money for the people who buy them, prolong treatment periods, exacerbate the conditions being treated, increase the emergence of drug resistance and can even cause death.

Special efforts have been undertaken to raise awareness of the importance of regulatory measures covering trade in products and starting materials, including active pharmaceutical ingredients and excipients, and implementation of good manufacturing practices.

Recommendations

- Countries are encouraged to implement the new WHO good trade and distribution practices, intended to improve safety in the trade of starting materials for pharmaceutical use.
- Member States are encouraged to implement a pilot phase of the new WHO certification scheme for pharmaceutical starting materials which will give additional information on the quality assurance system used in the production of starting materials.
- WHO should continue the Pre-qualification Project of medicines for priority diseases, particularly HIV, malaria and tuberculosis.
- WHO should foster collaboration between manufacturers and regulators in the implementation of GMP and provide training.
- WHO should continue to develop international guidelines for registration of multisource (generic) products.

Implications of regulatory decisions for pharmacoeconomics

The mandate of regulatory agencies is to promote and protect public health by ensuring that all medicines entering the market meet quality criteria, are safe and effective. The particular expertise of national regulatory authorities may make a valuable contribution to decisions on the cost effectiveness and rational use of medicines with regard to pharmacoeconomics and pricing. In countries with limited resources it is difficult to avoid direct involvement of national regulatory authorities in pharmacoeconomics due to their unique knowledge base.

Recommendations

- Where national regulatory agencies do not have pricing responsibilities, they should ensure that all information about safety and efficacy needed to conduct economic evaluation is made available to public bodies charged with reimbursement or pricing responsibilities.

- WHO should further support national regulatory authorities in introducing, wherever needed, elements which will contribute to pharmacoeconomic evaluation.

- WHO should carry out an analysis on the affordability of medicines, particularly in developing countries experiencing such problems. WHO should collect and make available to Member States information on various pricing options and mechanisms, examples of impact of inadvertent marketing strategies to medicines expenditure and potential public health implications of implementation of the TRIPS agreement.

- WHO should support pharmacoeconomic studies based on scientific methodology in countries and regions. Countries undertaking pharmacoeconomic studies are encouraged to present outcomes during the next ICDRA.

- Member States should study the potential of using objective measurement units such as defined daily doses (DDD) for monitoring drug utilization and using these data for developing rational national policies for pricing and increased access to essential medicines.

Current topics

The current topics session provides an opportunity to all regulators at the ICDRA to express their views on the newly-emerging topics which have not been reflected in the conference programme. Often, the topics raised in this session lead to substantial discussion during subsequent ICDRAs.

Recommendations

- The full flexibility of the TRIPS agreement to improve access to medicines should be explored by countries. Countries should not voluntarily exceed TRIPS obligations which could limit flexibility and utility in protection of national public health interests.

- Member States should consider the potential impact of usage patents on access and affordability of medicines.

- Countries should adopt the WHO Guidelines on Developing Measures for Combating Counterfeit Drugs, raise public and political awareness of the problem of counterfeiting, increase national and international cooperation, data exchange between all stakeholders, including national regulatory authorities, interested nongovernmental organizations, law enforcement agencies, industries, and relevant international organizations.

- WHO, in collaboration with other stakeholders, should develop a draft concept paper for an international convention on counterfeit drugs. WHO should convene a meeting of national regulatory authorities to discuss further the concept paper and related issues before the next ICDRA.

- The comparator product for a multisource (generic) medicine should be the first product registered in the market with a complete data file available. In case the originator is not available on the market and there is no multisource (generic) market leader, then other appropriate solutions should be considered on case by case basis.

- Doping in sports is a serious health problem and is within the remit of drug regulation. National regulatory authorities should remain vigilant and provide the necessary resources to combat such practices.

Associated events

Three meetings were held prior to the ICDRA. The Second Regional Workshop on Regulation of Traditional Medicines (see page 28); the Pan American Drug Regulatory Harmonization Initiative (PANDRH); and the pre-ICDRA Workshop on Counterfeit Drugs. This latter meeting was open to all interested parties, with over 90 participants from major institutions and agencies, including regulators, representatives of World Customs Organization, World Intellectual Property Organization and Interpol, industry representatives and NGOs. This workshop discussed the experience of various parties in fighting counterfeit drugs and debated the feasibility of drawing up an International Framework Treaty on Counterfeit Drugs.

Essential Medicines

Treating 3 million people living with HIV/AIDS by 2005

The World Health Organization (WHO) has launched a 3 by 5 strategy to treat three million people with HIV by 2005. The strategy will reflect the highest public health standards and will leverage resources and synergize action among interested stakeholders including Governments, institutions, agencies and programmes working with HIV-related activities at international, regional and local levels.

The 3 by 5 strategy recommends simplified HIV treatment regimens and expanded access to medicines. The strategy will ensure the supply of safe, effective and affordable medicines. WHO will assess the quality, safety and clinical efficacy of HIV medicines as single-drug, two-drug, and three-drug combination treatment through the WHO prequalification Project. A rigorous review process and ongoing quality monitoring will limit the entry of substandard and counterfeit medicines into the supply chain. In addition, the strategy will help build local regulatory and production capacity.

The current situation

HIV is rapidly spreading. It is on the rise again in Western Europe because integrated prevention and treatment programmes have not been sustained. Countries in Eastern Europe are home to the fastest-growing epidemic in the world which is crippling social and economic development. Over 1.5 million people are living with HIV in Eastern Europe and Central Asia, compared to only 30 000 in 1995. In Eastern Europe and Central Asia, only 7000 people receive antiretroviral therapy for HIV, which is 9% of those in need in the region. For many, the treatment is too expensive or simply not available.

WHO has also recently announced a plan to support the 3 by 5 strategy by expanding collaboration between national tuberculosis and HIV/AIDS programmes to curb the growing pandemic of TB/HIV co-infection, with a principal focus on Africa where 70% of the world's 14 million people who are co-infected live. A key element will be to rapidly expand voluntary HIV testing and counselling in TB programmes, with the aim of identifying and referring more than half a million TB patients who are HIV positive for treatment in the next two years. With additional training for health workers, TB programmes will also assist in HIV prevention, treatment distribution and patient care. Forty million people are currently infected with HIV, and 5 million more are infected every year. According to WHO, one third of the world's population is now infected with the TB bacillus, with more than 8 million people developing the active disease and 2 million dying of it each year.

3 by 5 country support

The Initiative will provide assistance to all countries that are committed to scaling up treatment. Ninety percent of those needing antiretroviral medicines are found in just 34 high-burden countries. Much of the work will focus on these countries.

Following a formal request by national authorities to the WHO Country Representative, an emergency fact-finding mission is made to each country. The mission includes WHO and UNAIDS staff, country and global partners. Planning will be carried out through the WHO Country Office, with support from HQ, the Regional Office and local UNAIDS missions to gain country and partner involvement and commitment.

Implementation of the strategy will immediately follow the emergency mission and continue through the years of the initiative and beyond 2005. Keeping 3 by 5 going will take perseverance, public support and international financial aid. A situation room will be built in WHO headquarters to monitor all progress in all aspects of implementation of 3 by 5.

Reference: Information obtained from various documents at http://www.who.int/3by5/en/ and www.who.int/medicines

AIDS medicines and diagnostics service

The AIDS medicines and diagnostics service (AMDS) is a mechanism created to expand access to quality, effective treatment for HIV/AIDS

by facilitating the increased supply of antiretrovirals (ARVs) and diagnostics in developing countries. The AMDS represents the access and supply arm of the 3 by 5 initiative, which aims to multiply eightfold the number of people in developing countries receiving antiretroviral therapy by 2005.

The AMDS builds on years of work by UNAIDS, WHO, UNICEF, the World Bank, and the global health community, as well as on some recent initiatives to address the AIDS treatment gap in developing countries. It brings together stakeholders and partners to maximize impact towards meeting the 3 by 5 goal as rapidly as possible.

What the AMDS will offer

Manufacturers currently have little idea of global market demand and its development over time. This situation affects both the price and volume of medicine production. AMDS will provide the necessary forecasting information to ensure that volumes produced reflect the real need at an affordable price.

The AMDS will offer technical support to countries to improve drug procurement, in-country supply management services, and local production where applicable. The AMDS will assist buyers to obtain best prices for individual or pooled demand for core ARVs and diagnostics. Where necessary, advice will be given on alternative sourcing options and through existing procurement agencies.

The AMDS will provide a service to governments, public interest and nongovernmental organizations (NGOs), health insurance and employer-benefit schemes, and other not-for-profit supply channels.

Specific services provided to countries

- Selection of ARVs, guidance on simplified treatment regimes, and selection of essential HIV diagnostic tests; country-level technical support to promote clinical guidelines and update the national essential medicines list.
- Patent status and licensing. Information on patent status of ARVs in the country; global guidance and country-specific support on the legal importation of generic medicines and voluntary/compulsory licensing.
- Registration and quality assurance. Global guidance and information on regulatory matters and registration status of ARVs; strengthening drug regulatory agencies in dealing with ARVs (registration, inspection, importation, local production and combination products).
- Global quality and product specifications for ARVs to be used for procurement tenders and contracts, including quality specifications for new combination products.
- Information on prequalification of ARVs and diagnostics, operational standards for evaluating supply agencies and quality control laboratories.
- Market intelligence on sources, prices, raw materials. Access to information on sources and prices of ARVs, other AIDS-related medicines and diagnostics, price indicators for raw materials for local production.
- Procurement of core ARVs and diagnostics. Global guidance and training programmes on procurement; practical information for buyers; access to the services of the WHO/UNAIDS diagnostics buyers group; country assessments and country-specific technical support to improve procurement and distribution of ARVs; access to global procedures to obtain economies of scale through international rate contracts; procurement services by or through AMDS.
- Import taxes and margins. Information on tariffs, taxes and margins in other countries; country-specific technical and political support in efforts to reduce them.
- Supply management and monitoring. Global guidance and training programmes in drug supply management and monitoring; country assessments and consultant support in improving national supply systems; methods and technical support in preparing institutional and national estimates of ARV quantities needed; full-time (inter)national technical staff to assist national authorities.
- Local production and quality assurance (Global guidance on good manufacturing practices (GMP) standards; training courses on quality assurance and GMP; technical support to the national drug regulatory agency in inspecting national production facilities.

Parallel to the medicines scheme (1), a project run by WHO and UNAIDS assesses the quality, safety and suitability of HIV diagnostics for use in

developing countries. Currently, 24 HIV test kits that have met the criteria are available at reasonable cost. Four of these are produced in transition economies. Information on the proprietary rights, licensing and patent issues related to these products is collected and made available.

WHO also evaluates CD4 and viral load tests to monitor the efficacy of HIV drug treatment and is helping countries to develop the skills to assess the quality of diagnostic technologies. WHO also provides training to health care workers to ensure correct use of diagnostic tests (2).

References

1. http://www.who.int/medicines and http://www.who.int 3by5/en/

2. http://www.who.int/eht

Fixed-dose combination therapy

WHO's Prequalification Project has added three new generic products for first-line HIV treatment to its list of medicines meeting WHO standards of quality, safety and efficacy. The products are fixed-dose triple therapy combinations containing lamivudine, stavudine and nevirapine. Their introduction in the list of prequalified medicines will increase choice and competition, thus contributing to make HIV treatment progressively more affordable.

The 3 by 5 strategy recommends simplified HIV treatment regimens so that countries can quickly expand access to antiretroviral medicines. These new products will help countries which are hardest-hit by the HIV epidemic get easy-to-take medicines to the people who need them most urgently. Single-pill combinations of antiretrovirals are a major breakthrough for treatment in poor countries as they improve the reliability and security of supplies, which has so far been one of the major obstacles to access. From a therapeutic point of view, they reduce the number of pills, are easier to take and promote greater patient compliance. They also ensure that the right dosage of each substance is given to the patient.

At present, the prequalification list contains over 50 single-drug, two-drug, and three-drug combinations, including the three newly qualified products. In assessing products and their manufacturers, prequalification provides a rigorous review process and ongoing quality monitoring. One of the benefits of this initiative is that it limits the entry of substandard and counterfeit medicines into the supply channels. In addition, the project helps build local regulatory and production capacity by involving local experts in the evaluations. Prequalification also respects intellectual property rights while reflecting the highest public health standards.

Reference: http://www.who.int/3by5/en/ and www.who.int/medicines0

HIV antiretrovirals and diagnostics funding

The Global Fund to Fight AIDS, Tuberculosis and Malaria, the World Bank, UNICEF and the Clinton Foundation have announced agreements that will make it possible for developing countries to purchase high-quality AIDS medicines and diagnostics at the lowest available prices, in many cases for more than fifty percent less than is currently available. Countries will be required to provide guarantees of payment, to conduct long term tenders and to ensure the security of drug distribution.

The Global Fund and the World Bank are among the world's largest sources of funding commitments to AIDS treatment. The Global Fund focuses more than 60 percent of the $US 2.1 billion committed for two years to 122 countries to the fight against AIDS. The World Bank has currently committed $US 1.6 billion to fight AIDS through the Multi-country HIV/AIDS Programs (MAP) and other AIDS operations, including grants for the poorest countries. UNICEF spent $US 111 million during 2003 in the fight against AIDS and is rapidly accelerating the procurement of antiretroviral medicines (ARVs) and AIDS diagnostic equipment and tests for developing countries.

The drugs in these agreements include individual formulations and two- and three-drug fixed dose combinations which have been prequalified by WHO to assure quality and efficacy. These medicines are critical components of the four regimens recommended by WHO as "first line" treatment for AIDS in its 3 by 5 initiative. In developing countries outside of Brazil, such life-sustaining therapy is available to fewer than 200 000 people living with HIV, although almost six million require it.

The pharmaceutical manufacturers included in these agreements are from South Africa and India. The price for the most common first line formulation under these agreements is as low as

$US 140 per person per year, one-third to one-half of the lowest price otherwise available in most settings. The diagnostic tests included in these agreements are offered by five leading medical technology companies and include CD4 tests and viral load tests. The prices available for these tests under the agreement include machines, training, reagents and maintenance and are up to 80% cheaper than otherwise available in the market.

Reference: http://www.clintonpresidentialcenter.com

World Bank ARV procurement manual

The *Technical guide for HIV/AIDS medicines and related supplies: Contemporary context and procurement* has been published by the World Bank. The Technical Guide was developed to address the specific requirements and unique features of the medicines and supplies that are part of the HIV/AIDS Care Package.

Project teams working on HIV/AIDS projects are strongly encouraged to use and disseminate the recommendations of the Guide. A dissemination strategy is under preparation .

Reference: http://siteresources.worldbank.org/intprocurement/Resources/Technical-Guide-HIV-AIDS.pdf

Research on new HIV microbicides

New antiviral agents are being developed by scientists and HIV experts from the UK Medical Research Council (MRC) and the Department for International Development (DFID). The antiviral properties of potential microbicides could work in a number of ways. They could kill or otherwise immobilize the virus, create a barrier to block infection, or prevent the infection from taking hold after it has entered the body. An effective microbicide would combine these mechanisms.

A large-scale trial is planned to evaluate the effectiveness of two of the six vaginal microbicides that are now in the final stages of clinical development. Updates on recent international microbicide research and development, including information on the first Phase III trials, will be released shortly.

Microbicides are likely to be of particular benefit to women who are increasingly bearing the brunt of the HIV epidemic and now account for over 50 per cent of people newly infected with HIV. Microbicides could potentially control the risk of contracting HIV and other sexually transmitted diseases.

Reference: http://www.mrc.ac.uk

Safety and Efficacy Issues

Safety of HIV therapies targeted by new advisory committee

An Advisory Committee on Medicinal Product Safety has been established under the auspices of WHO to respond promptly and efficiently to medicines safety issues of potential global importance. The first meeting of the Committee was held from 20–22 October 2003. Members are drawn from WHO Expert Advisory Panels and selected with regard to their experience in clinical pharmacology, pharmacovigilance, pharmacoepidemiology, clinical medicine, drug regulation, international public health, and risk-assessment. A report of the meeting is available on http://www.who.int/medicines.

The Committee has been set up to provide advice on policy and issues related to the safety and effectiveness of medicinal products in general and specific issues that:

- are important to national or international programmes;
- cannot be met by structures, institutions or systems in place;
- respond to identified needs of a country that may be beyond their capability; and
- advance and promote the future development of pharmacovigilance as a discipline.

During the meeting, discussion focused on how safety surveillance can strengthen the WHO 3 by 5 Initiative aimed to provide HIV treatment to three million people by 2005. It was agreed that patient safety issues should be integrated into the 3 by 5 initiative from the outset to ensure the most effective delivery of long-term benefits to patients and ensure success.

In 2002, the World Health Assembly urged Member States to establish and strengthen science-based systems for quality of care and patient safety, including the monitoring of medicines safety, using reporting systems and implementing measures to reduce risk.

The 3 by 5 initiative proposes the use of antiretroviral medicines (ARVs) for HIV treatment. There is already considerable experience of ARV use in industrialized countries and significant safety issues have been reported. However, there are a number of additional challenges facing developing countries targeted to receive ARVs, including:

- lack of an adequate infrastructure and trained health care professionals for monitoring of safety and use;
- complex co-morbid conditions including malnutrition, tuberculosis and other infectious diseases specific to HIV populations;
- use of alternative therapies and medicines and potential interactions;
- sociocultural and educational particularities and vulnerable populations; and
- lack of adequate regulatory systems or capacity to deal with safety outcomes.

Safety issues

Antiretrovirals have been associated with numerous adverse reactions, some of which may be serious. The outcome of long-term adverse effects is unknown. The reactions may be common or unusual, such as altered body fat distribution (lipodystrophy), hypersensitivity reactions, or muscle damage (myopathy) of the newborn. Besides causing harm to patients, these and other reactions may damage confidence in HIV treatment and reduce patient compliance and patients may stop taking life-prolonging ARVs. In the case of ARVs, poor compliance is known to lead to the development of resistance as well as therapeutic failure.

Contribution of patient safety strategies to public health programmes

There is evidence that knowledge and understanding of medicines safety through provision of public education improves patient compliance and confidence in public health programmes such as the 3 by 5 initiative. With efficient monitoring, better understanding of the safety of antiretrovi-

rals will lead to the development of improved treatment and a more rational use of existing therapies. Furthermore, once a basic monitoring infrastructure is in place, this can contribute to improved strategies for other public health programmes. The cost of a medicines safety system is small compared to the benefits gained in patient wellbeing and in reducing the costs of treating adverse reactions. The ultimate contribution that safety monitoring systems would make to international public health and clinical practice in the treatment of HIV disease are thus of high priority.

Resources a key to success

The following are a number of ways in which patient safety programmes can be integrated into the 3 by 5 initiative.

- Utilize the technical expertise of the WHO International Drug Monitoring Programme.
- Collaborate with existing national pharmacovigilance centres in the targeted countries.
- Call on expert advice on causality assessment and systematic data collection and sharing.
- Seek access to the WHO ADR database including information on drug-drug interactions.
- Educate, train and empower health professionals by improving access to medicine information resources.
- Use existing infrastructures for monitoring patient safety, such as for the Roll Back Malaria programme.
- Work with other organizations that have medicine safety experience in order to enhance patient communication and information.

It was also recognized that the pharmaceutical industry had a role to play by contributing experience and information on safety monitoring of HIV products and in implementing fully their own safety requirements.

There will be no delay in integrating a patient safety component into the 3 by 5 initiative, because it will build on existing medicines safety experience and framework. Additionally, the Advisory Committee will be available to advise on patient safety issues and activate the required support systems.

Conclusions

A well-defined patient safety programme is essential to the overall success of the 3 by 5 initiative by ensuring positive treatment follow-up. Medicines effectiveness and safety management is an essential and cost-effective means of maximizing the success of treatment interventions. Patients should be provided with health programmes that are structured and planned and that maximize health benefits while minimizing risk.

The risks and benefits of HRT

The Women's Health Initiative (WHI) study, a large randomized trial comparing combination hormone replacement therapy (HRT) to placebo, found that the increase in risk associated with long term therapy exceeded the benefits (1). In particular the promise of cardiovascular benefit from HRT was unfulfilled and therapy was found to increase the risk of cardiovascular events.

A further surprising result of the WHI study was an increase in the incidence of dementia with HRT using estrogen plus progestogen, and a failure to enhance cognitive function (2). The WHI study did, however, demonstrate protection against fracture with estrogen plus progestogen (1, 3) but this protection, even in women with the highest risk of fracture in the study, did not outweigh the other negative effects (3).

The Million Women Study (MWS), which had a prospective observational design, further emphasized the risks of HRT, indicating a higher risk of breast cancer with estrogen plus progestogen than with estrogen alone (4). The results indicated that the increase in the incidence of breast cancer with estrogen plus progestogen (compared to estrogen alone) was greater than the reduction in incidence of endometrial cancer associated with adding progestogen to oestrogen therapy (4). The MWS also reported a significant increase in the incidence of breast cancer with tibolone and with implanted and transdermal estrogen-only preparations.

Following its comprehensive review of these studies and other available data, the Australian Drug Evaluation Committee (ADRAC) has recommended "The use of HRT for any long term disease prevention cannot be generally justified as the potential harm may outweigh potential benefits. This concern also applies to the use of HRT to prevent osteoporosis.

"HRT has an established place in the short term management of symptoms of the menopause. For treatment of established osteoporosis, the selection of HRT by the patient and doctor should be based on a careful consideration and discussion of risks and benefits for that individual."

In addition, ADRAC advises that HRT use be for as short a time as practical, and be reviewed regularly.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 23, Number 2, April 2004

References

1. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association,* **288**: 321–333 (2002)

2. Shumaker, S.A., Legault, C., Rapp, S.R. et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative Memory Study: a randomized controlled trial. *Journal of the American Medical Association*, 289: 2651–2662 (2003).

3. Cauley, J.A., Robbins, J., Chen, Z. et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density. The Women's Health Initiative randomized trial. *Journal of the American Medical Association*, 290:1729–1738 (2003).

4. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*, **362**: 419–427 (2003).

Macrolides and warfarin interaction

The Australian Drug Evaluation Committee (ADRAC) has received reports of interactions between warfarin and all four macrolide antibiotics (azithromycin, clarithromycin, erythromycin, and roxithromycin) (see table below) (1). Although most cases were asymptomatic, some reports documented substantial increases in INR. The haemorrhagic complications reported included haematoma, haemoptysis, haematuria, melaena, and retroperitoneal haemorrhage.

Close attention should be paid to INR monitoring in patients taking warfarin who are commenced on a macrolide antibiotic. Consideration could also be given to the use of an alternative antibiotic if possible. Azithromycin has a particularly long half-life (around 68 hours), so that an interaction with warfarin may theoretically persist for some days after azithromycin has been ceased.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 23, Number 2, April 2004

Reference

1. *Australian Adverse Drug Reactions Bulletin*, **14**: 11 (1995).

Statin risk factors: myopathy and rhabdomyolysis

Four statins (HMG CoA inhibitors) are available in Australia for the treatment of hypercholesterolaemia: simvastatin, atorvastatin, pravastatin and fluvastatin. Each of the statins may cause myalgia or rhabdomyolysis. Cerivastatin was removed from the market worldwide because of an unacceptably high rate of rhabdomyolysis, including fatal cases, particularly when used with gemfibrozil (1).

The rates of muscle disorders observed in clinical trials of statins have not been significantly different from those with placebo (2), but wider clinical use involves individuals having multiple disease states or taking potentially interacting medication. Recent reviews indicate that factors

Table: ADRAC reports of macrolide-warfarin interaction

Drug	reports (no. symptomatic)	onset in days (median range)	INR (median)
azithromycin	3 (0)	3; 2-5	9.6
clarithromycin	6 (2)	7; 0-9	7.6
erythromycin*	19 (4)	5; 0-18	9.7
roxithromycin	56 (27)	6; 0-36#	8.8

* metronidazole was another potentially interacting agent in 2 cases. # onset > 1 year in a further patient.

which increase the plasma concentrations of statins are associated with an increase in the risk of myalgia, myopathy and, particularly, rhabdomyo-lysis (3, 4). For simvastatin and atorvastatin which are metabolized by the liver enzyme CYP3A4 these factors are presented in Table 1 below.

Over half of the simvastatin cases with rhabdomyolysis had more than one identified risk factor (see Table 2). Individuals with several risk factors may be at risk of developing rhabdo-myolysis, rather than a less serious muscle disorder. A feature of the cases of rhabdomyolysis is that long-term statin therapy was well tolerated until after a change in medication (e.g. increase in the dose of statin, or addition of clarithromycin or diltiazem).

Pravastatin and fluvastatin are not metabolized by CYP3A4 and are less subject to increases in plasma concentration by interaction with other drugs. Reports of muscle disorders with these statins are shown below. The dominant risk factors for pravastatin and fluvastatin were advanced age and high dose. The lower number of cases of rhabdomyolysis with these statins is probably associated with the lesser likelihood of drug interaction, but is also related to the lower usage in Australia (From 1992 to November 2003, 85% of statin prescriptions have been for simvastatin or atorvastatin).

High doses of statins should be used with caution in the elderly, in patients with renal or hepatic insufficiency, hypothyroidism or diabetes. Particular caution should be observed in patients taking simvastatin or atorvastatin with these conditions, if gemfibrozil, cyclosporine or diltiazem are being taken concomitantly. Consideration should be given to temporary discontinuation of simvastatin or atorvastatin, if short-term macrolide antibiotic or azole antifungal therapy is required. Patients should be advised to report to their doctor if muscle aches, pains or weakness develop.

Table 1: Factors increasing the risk of muscle disorders with simvastatin and atorvastatin

Substances inhibiting metabolism by CYP3A4	cyclosporin, diltiazem, verapamil, macrolide antibiotics, azole antifungals, protease inhibitors, grapefruit juice
Medicine inhibiting metabolism by other means	gemfibrozil
Disease states	diabetes, hypothyroidism, renal and hepatic disease
Advanced age	≥ 70 years
High statin dose	≥ 40 mg/day

Table 2: Frequency of risk factors in ADRAC reports of muscle disorders with the statins

Statin	Total reports	Myalgia/ myopathy/ CK increase	% with risk factors	Rhabdo-myolysis	% with risk factors
Simvastatin	2493	518	37%	91	94%
Atorvastatin	1055	237	45%	26	73%
Pravastatin	442	99	41%	5	80%
Fluvastatin	248	68	4%	2	100%

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 23, Number 1, February 2004

Previous information on statins in primary prevention has been presented in WHO Drug Information, Volume 17, No. 3, p.156

References

1. *Australian Adverse Drug Reactions Bulletin*, **20**(1): 3 (2001).

2. Gotto, A.M. Safety and statin therapy. *Archives of Internal Medicine*, **163**: 657–659 (2003).

3. Thompson, P. D., Clarkson, P, Karas, R.H. Statin-associated myopathy. *Journal of the American Medical Association*, **289**: 1681–1690 (2003).

4. Ballantyne, C.M., Corsini, A., Davidson, M.H. et al. Risk for myopathy with statin therapy in high risk patients. *Archives of Internal Medicine,* **163**: 553–564 (2003).

Serotonin syndrome

Serotonin syndrome is caused by excessive central nervous system and peripheral serotonergic activity. It most commonly occurs with a combination of serotonergic agents, but may also occur with a single agent. A combination of agents increasing serotonin by different mechanisms, such as by inhibition of serotonin uptake and serotonin metabolism, is associated with a high risk of the syndrome (see Table 1) (1).

Serotonin syndrome is a clinical triad of cognitive-behavioural changes, autonomic dysfunction and neuromuscular dysfunction. At least three of the features listed in Table 2 must be present (1, 2). There is no laboratory test to aid diagnosis. The syndrome often occurs within a day of a change in treatment (increase in dose or addition of another serotonergic agent) and the evolution of symptoms is rapid. It should not be confused with neuroleptic malignant syndrome which is clinically similar, but is an idiosyncratic response to neuroleptic agents, usually occurs after longer periods of treatment and develops over a period of days or weeks (1).

The Australian Drug Evaluation Committee (ADRAC) has received 161 reports of serotonin syndrome. The majority describe the syndrome in association with the concomitant use of two or more serotonergic agents, in particular SSRIs (68), tramadol (29), moclobemide (23), venlafaxine (18), tricyclic antidepressants (18) and St John's wort (8). In 61 reports, the serotonin

Table 1: Agents causing serotonin syndrome

Antidepressants	SSRIs, monoamine oxidase inhibitors (including moclobemide), tricyclics, mirtazapine, venlafaxine
Antiparkinson	Amantadine, bromocriptine, levodopa, selegiline, carbergoline, pergolide
Illicit drugs	Cocaine, hallucinogenic amphetamines such as MDMA (ecstasy), LSD, etc.
Migraine therapy	Dihydroergotamine, naratriptan, sumatriptan, zolmitriptan
Other agents	Tramadol, carbamazepine, lithium, reserpine, sibutramine, St. John's wort, bupropion, pethidine, morphine

Table 2: Clinical features of serotonin syndrome

Cognitive-behavioural changes	agitation, mental status changes (confusion, hypomania)
Autonomic dysfunction	sweating, diarrhoea, fever, shivering, hypertension
Neuromuscular dysfunction	hyperreflexia, incoordination, myoclonus, tremor

syndrome developed in association with a single agent: SSRIs (40), moclobemide (5), venlafaxine (5) and tramadol (5 reports) (3).

Serotonin syndrome is potentially serious. Reports to ADRAC have described confusion (31), convulsions (23), hypertension (22), hallucinations (12) and delirium (7). In the majority of reports, the signs and symptoms developed within 24 hours of the addition of another serotonergic agent or an increase in dose of an agent. Patients responded to withdrawal of the serotonergic agent(s) and appropriate treatment. Recovery was documented in 85% of the cases where the outcome was known and the remainder of patients had not recovered at the time of reporting.

Health professionals should note the drugs that may cause serotonin syndrome, alone or in combination with other serotonergic agents, and be alert to the features of serotonin syndrome. Patients should be informed of the risk and symptoms of serotonin syndrome when serotonergic agents are prescribed.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 23, Number 1, February 2004

References

1. Langford N.J. Serotonin Syndrome. Adverse *Drug Reaction Bulletin*, No. 217, December 2002.

2. Sternbach H. The serotonin syndrome. *American Journal of Psychiatry, 148:* 705–713 (1991).

3. Tramadol and serotonin syndrome. *Australian Adverse Drug Reactions Bulletin*, **21**: 14 (1991).

Antidepressants: worsening depression and suicidal behaviour

The US Food and Drug Administration (FDA) has asked manufacturers to include a warning statement recommending close observation for worsening depression or the emergence of suicidality of adult and paediatric patients treated with the following antidepressants: fluoxetine (Prozac®); sertraline (Zoloft®); paroxetine (Paxil®); fluvoxamine (Luvox®); citalopram (Celexa®); escitalopram (Lexapro®); bupropion (Wellbutrin®); venlafaxine (Effexor®); nefazodone (Serzone®); and mirtazapine (Remeron®).

Warning Information

- Health care providers should carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose either increases or decreases.
- Heath care providers should carefully evaluate patients in whom depression persistently worsens, or emergent suicidality is severe, abrupt in onset, or was not part of the presenting symptoms, to determine what intervention, including discontinuing or modifying the current drug therapy, is indicated.
- There is concern that patients who experience symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania may be at increased risk for worsening depression or suicidality. Therefore, therapy should be evaluated and medications may need to be discontinued when symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.
- If a decision is made to discontinue treatment, certain of these medications should be tapered rather than stopped abruptly.
- Patients should be adequately screened to determine if they are at risk for bipolar disorder before initiating antidepressant treatment.

Among antidepressants, only fluoxetine is approved for the treatment of paediatric major depressive disorder. Fluoxetine, sertraline, and fluvoxamine are approved for paediatric obsessive compulsive disorder. None of these drugs is approved as monotherapy for use in treating bipolar depression, either in adults or children.

Reference: *FDA Public Health Advisory,* 22 March 2004.

Use of SSRI antidepressants in children and adolescents

The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has considered the safety and efficacy of selective serotonin reuptake inhibitor (SSRI) antidepressants in children and adolescents. There is international concern about a possibility of increased suicidal ideation and self-harm behaviour provoked by the use of these drugs for the treatment of major depressive disorder (MDD).

It should be noted that none of the SSRIs is approved for the treatment of MDD in children or adolescents in Australia, but these drugs are being used for this purpose. Two SSRIs (fluvoxamine and sertraline) are approved in Australia for the treatment of obsessive-compulsive disorder (OCD) in children and adolescents.

ADRAC considers that the current data are not conclusive regarding the efficacy and safety of SSRIs in MDD in children and adolescents. With this in mind, ADRAC recommends:

1. Any SSRI use in children and adolescents with MDD should be undertaken only within the context of comprehensive management of the patient. Such management should include careful monitoring for the emergence of suicidal ideation and behaviour.

2. The choice of an SSRI for children or adolescents with MDD should be made only after taking into account the recent evaluations of clinical trial data and the Product Information.

3. Children and adolescents who are currently being treated for MDD with an SSRI should not have their medication ceased abruptly.

Reference: Statement from the Adverse Drug Reactions Advisory Committee, 11 March 2004 on http://health.gov.au/tga/

Repaglinide and gemfibrozil interaction

An interaction between repaglinide a short-acting secretagogue and gemfibrozil a lipid-lowering agent used to great dyslipidaemia has been reported (1) in the Volume 29 of *Current problems in Pharmacovigilance* (Committee on Safety of medicines, United Kingdom). When administered concomitantly, the blood glucose-lowering effect of repaglinide may be markedly enhanced and prolonged.

Worldwide, 5 spontaneous reports have been received of serious hypoglycaemia episodes in patients using repaglinide and gemfibrozil together. Three of these patients experienced hypoglycaemic coma, one of whom died. In some cases, the patients were also taking other drugs and it is therefore not known whether the reactions can be solely attributed to an interaction with gemfibrozil. There have been no reports of this interaction in the United Kingdom.

Any change in repaglinide pharmacokinetics caused by concomitant gemfibrozil administration is likely to be via inhibition of cytochrome P450 2C8. Other inhibitors of this enzyme such as trimethoprim, may also enhance the effect of repaglinide.

Because of this interaction, co-administration of repaglinide and gemfibrozil is contraindicated. Based on known metabolism of lipid-lowering agents, a similar interaction between repaglinide and other lipid-lowering agents is not expected.

Reference

1. Niemi, N. *Diabetologia*, **46** (3): 347–351 (2003).

Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and unexpected adverse drug reactions. A signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information". All signals must be validated before any regulatory decision can be made.

Vaccines and Biomedicines

World's biological experts establish standards

The WHO Expert Committee on Biological Standardization met in Geneva from 17 to 21 November 2003. The technical specifications and reagents developed by the Committee define international regulatory expectations for the quality, safety and efficacy of biological pharmaceutical products, including vaccines, blood products, biological therapeutics and in vitro diagnostic devices. This information is targeted to national regulatory authorities and manufacturers. A full report of the Committee's decisions is in preparation and will be published in the WHO Technical Report Series. In the meantime, a prepublication document has been posted onto the WHO website to provide early notice of content (1).

The Committee recommended establishment of the following new documents.

Guidelines on nonclinical evaluation of vaccines: regulatory expectations

A broad range of novel vaccines are under development and there is a need for guidance on the type and extent of their nonclinical evaluation since this forms an essential part of the quality assessment of a vaccine candidate. The guidelines are intended to set out principles for nonclinical evaluation of vaccines and provide information and guidance to vaccine manufacturers, and recommendations for national regulatory authorities concerning evaluation and assessment. The document is intended to complement *WHO Guidelines for clinical evaluation of vaccines: regulatory expectations* (2).

Recommendations for the production and quality control of pneumococcal conjugate vaccines

Infections caused by *Streptococcus pneumoniae*, are responsible for substantial morbidity and mortality, particularly in the very young and elderly. Several pneumococcal vaccines containing polysaccharide conjugated to protein carriers are now available or at an advanced stage of development. Controlled clinical trials with these vaccines have demonstrated that such conjugates are both safe and highly immunogenic. Differences in the incidence of serotypes causing disease from one continent to another has lead to the development of pneumococcal vaccine formulations consisting of increasing numbers of conjugated components. Experience gained with identification of reference levels of antibodies supporting successful licensing of a product in a number of countries will guide the review of clinical trial data from other countries and with other products.

Recommendations for the production and quality control of pneumococcal conjugate vaccines takes account of the large number of serotypes of *S. pneumoniae* and the need to allow flexibility in recommendations to cover different conjugation chemistries and carrier proteins.

Production and quality control of inactivated influenza vaccine

Guidelines on production and quality control of inactivated influenza vaccine have been updated following an informal WHO Consultation in July 2003. Significant development in influenza vaccines has taken place since the last revision of the document. Subunit and split vaccines are now widely used and the effective dose of haemag-

**Fifty-fourth meeting of the WHO Expert Committee on Biological Standardization, 17–21 November 2003, Geneva. Participation included members from: Belgium, Canada, France, Indonesia, Republic of Korea, Mexico, Netherlands, Russian Federation, Switzerland, United Kingdom, United States of America. Representatives from: Global Collaboration of Blood Safety, European Diagnostic Manufacturers Association, Council of Europe, Developing Country Vaccine Manufacturers Network, European Plasma Fractionation Association, International Association of Biologicals, International Bureau of Weights and Measures, International Federation of Clinical Chemistry and Laboratory Medicine, International Federation of Pharmaceutical Manufacturers Associations, International Society on Thrombosis and Haemostatis, Plasma Protein Therapeutics Association, United States Pharmacopeia.*

glutinin has been established. In addition, vaccines containing adjuvants have been developed and approved. The danger exists of pandemics caused by the appearance of novel and highly pathogenic strains of virus and this danger presents a number of challenges for production and administration of suitable vaccines. The new recommendations reflect these and other developments.

Diphtheria, tetanus, pertussis and combination vaccines

Developments have taken place in methods of assay of diphtheria and tetanus vaccines directed to overcoming difficulties in potency testing including a number of in vitro assays. A series of reviews and meetings held during 1999–2000 resulted in proposals for amendment of the WHO Requirements but the technical details could not be finalized at that time. Further discussion resulted in a recommendation to move to a harmonized and simplified batch release assay using guinea pigs. The main changes to the present requirements constitute an updating of the sections on reference materials and separation of sections on potency into two, addressing licensing and batch release respectively.

Use of animal cells for the in vitro production of biologicals

The *WHO Requirements for the use of animal cells as in vitro substrates for the production of biologicals* (3) provide information on a WHO cell bank of Vero cells. These cells were designated as a master cell bank in 1998 making cultures of the cells available to manufacturers and national control authorities. Possible deficiencies in the records relating to the cell bank might have regulatory implications for establishment of master cell banks, and so a revision of the requirements was proposed. The Committee endorsed a recommendation from a WHO Cell Bank Monitoring Group that the 10–87 Vero cell bank should not be considered as a master cell bank for direct use in manufacturing processes. Rather, the 10–87 bank should be regarded as a Cell Seed qualified by scientific analytical consensus from which master cell banks may be established for thorough re-qualification.

International Reference Materials

A list of new or replacement reference materials is given in Table 1. Details of selected reference materials are given below to illustrate the range of issues considered by the Committee.

Yellow fever vaccine

Potency determination of yellow fever vaccines has historically been based on mouse LD^{50} assays although in vitro plaque assays have been available and in routine use for some years. The need to improve standardization of yellow fever potency determinations led to a collaborative study performed by thirteen laboratories in eight countries to assess the suitability of candidate preparations for an International Standard and the relationship between the two assay methods. On the basis of the results of the collaborative study, the Committee established a preparation, in ampoules coded 99/616, as the First International Standard for Yellow Fever Vaccine.

Data obtained in the study indicated that there was a consistent relationship between mouse and plaque assays. The Committee therefore supported a proposal to encourage manufacturers and control laboratories to include the standard in assays to evaluate its suitability for setting a minimum potency of $10^{4.0}$ IU for yellow fever vaccines. Data should be collated by WHO and analysed to determine whether the potency specification given in the WHO Recommendations (4) should be amended.

Factor VIII, concentrate

Stocks of the current (recombinant) standard are likely to be exhausted within 12 months and there have been reports of difficulties in using recombinant material in assaying plasma-derived concentrates. For these reasons, and after extensive consultation, it has been decided that plasma-derived factor VIII will be the replacement material. A collaborative study among 38 laboratories in 21 countries to establish a common batch reference preparation was conducted and the Committee established the Seventh International Standard for Factor VIII, Plasma-derived, Concentrate, in ampoules coded 99/678, and an activity of 11.0 IU per ampoule.

Human interferon beta

The current International Standard for interferon beta is an impure preparation derived from human fibroblasts containing about 1% interferon. Other cytokines present influence the results of some assays. Accordingly, an extensive collaborative study of new and existing reference preparations for interferon beta has been performed by 16 laboratories in 8 countries. One candidate preparation, consisting of glycosylated interferon beta derived from Chinese hamster ovary (CHO) cells, gave a smaller inter-laboratory variability,

compared with the current standard, with all but one sample examined. The Committee established the Third International Standard for Interferon Beta, Human, Recombinant, Glycosylated, in ampoules coded 00/572, and assigned a potency to it of 40 000 International Units per ampoule. Since stocks of the current standard remain, the Committee formally disestablished the Second International Standard for interferon beta, fibroblast, human, code number Gb23-902-531. The CHO-cell derived material is likely to continue to be available and is more suitable for calibration of future therapeutic products than the fibroblast material. However, it is not suitable for assay of the Ser-17 interferon beta analogue and the 1st International Standard of interferon-beta Ser 17 mutein, Gxb02-901-535, will be retained.

Hepatitis B surface antigen

Because the current First International Standard for hepatitis B surface antigen is in need of replacement, a candidate and panel of dilutions were proposed. The aim of these reference materials is to aid regulatory authorities and manufacturers of HBsAg test kits in measuring analytical kit sensitivity by providing a standard with an internationally accepted unitage.

WHO collaborative studies were conducted and data demonstrated that the assigned values of the different HBsAg reference preparations differ considerably: 1 IU is equivalent to 0.58 PEI units (primary) or 0.43 PEI units (current) or 1.9 French 'ng' or 5.6 Abbott 'ng'. However, it is noteworthy that in 1985, the relationship between IS and the primary PEI was nearly the same as was found in the current study: 1 IU = 0.55 PEI unit. This and related biochemical data indicate that there has been no drift in the IU over 18 years. Furthermore, the study showed that the prediluted panel provides a convenient resource for authorities to assess sensitivity, especially of rapid tests.

On the basis of the results obtained, the Committee established the candidate preparation as the Second International Standard for Hepatitis B surface antigen, in vials coded 00/588, with an assigned value of 33 IU per vial. The Standard contains antigen subtype adw2, genotype A. The Committee also established panel members A to D, in vials coded 01/400, 01/402, 01/404 and 01/406, which are 1 in 4, 1 in 16, 1 in 64 and 1 in 256 dilutions of the International Standard respectively, and panel member E, in vials coded 00/616, which consists of human re-calcified plasma, as a reference panel for hepatitis B surface antigen for use by national regulatory authorities in the assessment of the sensitivity of assay kits for the detection of the surface antigen.

Quality, safety and efficacy of biological medicines

Wild poliovirus contamination of oral poliomyelitis vaccine

In the period November 2002 to February 2003, several cases of poliomyelitis were observed in one country after vaccination and the MEF-1 reference wild-type poliovirus type 2 strain was isolated in each case (5). Initial investigations excluded cross-contamination within the diagnostic WHO polio laboratory network that cultured the viruses as an explanation for the findings. Further examination demonstrated the presence of MEF-1 in vials of one vaccine batch that had been filled locally from imported bulk material. Samples of the batch that had been collected from the field, from retained samples and from other bulks were tested. Only samples from the field were positive so that contamination had taken place downstream from manufacture although it could not be established whether this was during storage or distribution. Enhanced security measures have now been put in place by the manufacturer concerned.

The Committee was asked to consider the wider implications of this episode; whether current WHO GMP guidance is adequate and whether additional control measures on the final product should be laid down. The Committee considered that prevention of deliberate interference with a product requires safeguards different to normal GMP and that no changes to existing GMP guidance for this reason were necessary. However, the Committee drew attention to measures that ensure that vials are tamper-proof and to procedures that are available to detect counterfeiting. In this context WHO was advised to obtain additional specialist advice, and to make this available to all vaccine manufacturers, their distributors and national regulatory authorities.

References

1. http://www.who.int/biologicals

2. World Health Organization. *Expert Committee on Biological Standardization*. Technical Report Series, No. 924 (in press)

Table 1. New or replacement International Standards established by the Fifty-fourth WHO Expert Committee on Biological Standardization

ADDITIONS

Antibodies

anti-toxoplasma IgG, human	20 IU/ampoule	First International Standard 2003

This substance is held and distributed by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar, Herts. EN6 3QG, England.

Antigens and related substances

yellow fever vaccine	$10^{4.5}$ IU/ampoule	First International Standard 2003
pertussis toxin	10 000 IU/ampoule	First International Standard 2003

These substances are held and distributed by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar, Herts. EN6 3QG, England.

Blood products and related substances

Factor VIII, concentrate, plasma, human	11.0 IU/ampoule	Seventh International Standard 2003
Factor VIII/von Willibrand Factor, plasma, human	0.68 IU/ampoule Factor VIII:C 0.94 IU/ampoule Factor VIII:antigen 0.91 IU/ampoule VWF:antigen 0.78 IU/ampoule VMF:ristocetin cofactor 0.94 IU/ampoule VWF: collagen binding	Fifth International Standard 2003
prekallikrein activator, human	29 IU/ampoule	Second International Standard 2003
low molecular weight heparin	1097 IU/ampoule Anti-Xa 326 IU/ampoule Anti-IIa	Second International Standard 2003

These substances are held and distributed by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar, Herts. EN6 3QG, England.

Table 1. New or replacement International Standards Continued

Cytokines, growth factors and endocrinological substances		
Interferon, beta, human, recombinant, glycosylated	40 000 IU/ampoule	Third International Standard 2003
tumour necrosis factor, Aapha, human, recombinant	46 500 IU/ampoule	Second International Standard 2003
luteinizing hormone, human recombinant	189 IU/ampoule	First International Standard 2003
thyroid-stimulating hormone, human, for immunoassay	11.5 x 10^{-3} IU/ampoule	Third International Standard 2003
These substances are held and distributed by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar, Herts. EN6 3QG, England.		
Diagnostic reagents		
hepatitis B surface antigen	33 IU/vial	Second International Standard 2003
hepatitis B surface antigen panel (set of 4 dilutions and control)	No assignment	First International Reference Panel 2003
These substances are held and distributed by the International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar, Herts. EN6 3QG, England.		
lipoprotein (a) for immunoassay	0.107 nanomoles/vial	First Reference Reagent 2003
This substance is held and distributed by Northwest Lipid Research Laboratories, University of Washington School of Medicine, 2121 North 35th Street, Seattle, WA 98103, USA.		

3. World Health Organization. *Expert Committee on Biological Standardization*.Technical Report Series, No. 878, Annex 1 (1998).

4. World Health Organization. *Expert Committee on Biological Standardization*.Technical Report Series, No. 872, Annex 2 (1998).

5. *Weekly Epidemiological Record*, **78**: 88 and 284 (2003)

Herbal Medicines

Regulation of traditional medicines in Africa

The majority of African populations use traditional medicine for their health care needs which is often bought in places such as open markets and local stores. Although many traditional medicines are claimed to cure various diseases, scientific evidence of safety, efficacy or quality is lacking and most countries in sub-Saharan Africa have no regulation, safety-monitoring or pharmacovigilance centres for the pharmaceuticals or herbal products sold on their markets. As with conventional medicines, this lack of regulatory control will compound the risks to patients. In view of this situation, the WHO Regional Committee for Africa has adopted the Regional Strategy on Traditional Medicine which urges Member States to develop systems for the safety, efficacy and quality of traditional medicines.

In order to support Member States to facilitate the evaluation of traditional medicines for registration purposes, the WHO Regional Office for Africa, organized the first Regional workshop on Regulation of Traditional Medicines in Johannesburg, in April 2003 in collaboration with the Department of Essential Drugs and Medicines Policy in WHO Geneva. The workshop was attended by 18 national drug regulatory authorities and experts from: Benin, Burkina Faso, Congo, Cote d'Ivoire, Ghana, Ethiopia, Kenya, Madagascar, Mali, Mozambique, Nigeria, South Africa, Swaziland, United Republic of Tanzania, Uganda, Zambia and Zimbabwe. The document *Guidelines on Registration of Traditional Medicines in the WHO African Region* was reviewed and adopted at that workshop.

The Second Regional Workshop on Regulation on Traditional Medicines has been organized in Madrid, Spain, 13–14 February 2004, with the objective of promoting the registration and marketing of safe, effective and good quality traditional medicines within the African Region. The workshop was organized by WHO with support from the Spanish Agency for Medicines and Health Products in Madrid, Spain.

The purpose of the Second Regional Workshop was to expand WHO's support in building capacity to regulate herbal medicines in countries of the WHO African Region, according to their national situation. *Guidelines on Registration of Traditional Medicines in the WHO African Region* were presented at the workshop which brought together 15 invited national drug regulatory authorities and experts from Angola, Burkina Faso, Cameroon, Congo, Ghana, Lesotho, Liberia, Madagascar, Namibia, Niger, Nigeria, Sierra Leone, Togo and Zimbabwe. This workshop also provided an opportunity for participants to attend the Eleventh International Conference of Drug Regulatory Authorities (See page 3). Against this framework, the workshop focused on three themes:

- Regulation and registration of traditional medicines,
- Quality control of traditional medicines, and
- Safety monitoring and pharmacovigilance of traditional medicines.

Recommendations

The Workshop identified major challenges and made recommendations for each of the three themes as follows.

Major challenges include:

- Lack of national policies and legal framework on traditional medicine in most countries of Africa.
- Lack of registration of herbal medicines.
- Difficulty in evaluating the safety and efficacy of traditional medicines.
- Lack of minimum regulatory requirements for safety and efficacy of traditional medicines.
- Lack of methodology and tools for evaluation of traditional medicines particularly lack of information on clinical data.
- Lack of understanding by traditional health practitioners on the need for regulation of traditional medicines.

• Lack of protection of medicinal plant and traditional medical knowledge.

Recommendations for Member States

1. Member States should adopt WHO guidelines related to national policy, legal framework, and code of ethics, regulation and registration of herbal medicines and formulate appropriate national policies.

2. Member States should establish/strengthen legal frameworks to back up the national policy on traditional medicine.

3. Member States should set up a communication network between national drug regulatory authorities and associations of traditional health practitioners.

4. Member States should undertake a listing of traditional medicines in circulation within their countries.

5. Member States should adopt and implement a WHO Regional framework on protection of traditional medical knowledge and intellectual property rights of traditional medicine.

6. Member States should develop a national inventory of commonly used medicinal plants.

Recommendations to WHO and partners

WHO and partners should support Member States to:

• formulate national policies on traditional medicine.

• develop strategy to implement the regulation of traditional medicine.

• develop inventories of traditional medicinal products in circulation within the countries.

Quality control of traditional medicines

Major challenges include:

• Lack of expertise in quality control of herbal medicines among national drug regulatory authorities.

• Inadequate laboratories and equipment for quality control of traditional medicines.

• Lack of pharmacopoeia of national medicinal plants for quality control of traditional medicines.

Recommendations for Member States

1. Member States should strengthen human resources capacity to undertake quality control of herbal medicines.

2. Member States should adopt and implement *WHO guidelines on Good Agricultural and Collection Practices of Medicinal Plants* and *Good Manufacturing Practices for Herbal Medicines.*

3. Member States should develop national monographs/pharmacopoeia of medicinal plants and share this information. The use of WHO monographs, African Pharmacopoeia and other national monographs for quality control should also be encouraged.

4. Member States should strengthen national quality control laboratories to be able to control the quality of herbal medicines or set up a network with other domestic research institutes which have a capacity to carry out quality control of herbal medicines.

5. If needed, Member States could use Regional quality control laboratories from neighbouring countries through WHO country and Regional Offices for Africa.

6. Member States should strengthen communication amongst national drug regulatory authorities and between them and importing and exporting countries of herbal medicines.

Recommendations to WHO and partners

1. WHO and partners should:

• support countries to strengthen the capacity of countries for quality control.

• support countries to undertake an inventory of medicinal plants commonly used in their communities.

• support countries to develop their national pharmacopoeia or monographs of medicinal plants.

Safety monitoring and pharmacoviglance

Major challenges:

Most countries in the WHO African Region have no safety monitoring or pharmacovigilance system for essential or herbal medicines.

Recommendations for Member States

1. Member States should set up a safety monitoring and pharmacovigilance system and the expand existing system to cover safety monitoring and pharmacovigilance of herbal medicines.

2. Member States should control advertisements of herbal medicines.

3. Member States should develop consumer educational information on the proper use of traditional medicines.

Recommendations to WHO and partners

1. WHO and partners should

- support Member States to develop consumer educational information on the proper use of traditional medicines.

- facilitate communication between Member States of the WHO African Region and WHO Collaborating Centre for Safety Monitoring in Uppsala, Sweden.

- support requests on human resource development in safety monitoring of herbal medicines.

Besides the above-mentioned recommendations, Member States proposed that WHO organize an African Conference of Drug Regulatory Authorities on Herbal Medicines every two years.

Conclusion

The Regional workshop facilitated sharing of information on the minimum regulatory requirements for the assessment of the quality, safety and efficacy of traditional medicines with respect to their registration as laid down in the *Guidelines for Registration of Traditional Medicines in the WHO African Region; and*

The Workshop also made a review of the regulatory status of traditional medicine including the results of the global survey on regulation of herbal medicines and national policy on TM/CAM at both regional and global levels.

The Workshop also discussed the impact of the WHO guidelines on *Good Agricultural and Collection Practices of Medicinal Plants and Safety Monitoring and Pharmacovigilance of Herbal Medicines* (see below).

Herbal medicines, patient safety and plant conservation

WHO has published guidelines for good agricultural and collection practices for medicinal plants intended for national governments, to ensure production of herbal medicines is of good quality, safe, sustainable and poses no threat to people or the environment.

Herbal medicines are the natural answer to many ailments and are often locally available. For this reason, their use remains widespread and they are popular in many countries. Because of improved monitoring, reports of patients experiencing adverse reactions with use of herbal medicines are on the rise. Major causes of adverse events can be directly linked to poor quality, particularly of raw medicinal plant materials, or to the wrong identification of plant species. Cultivating, collecting and classifying plants correctly is therefore important.

In addition to patient safety issues, there is the risk that a growing herbal market might pose a threat to biodiversity through over-harvesting of raw materials needed in herbal and traditional medicines and other natural health care products. If not controlled, these practices may lead to the extinction of endangered species and the destruction of natural habitats and resources.

The *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants* are an important initial step to ensuring provision of good quality, safe herbal medicines and ecologically sound cultivation practices for future generations. The Guidelines cover the spectrum of cultivation and collection activities, including site selection, climate and soil considerations and identification of seeds and plants. Guidance is also given on the main post-harvest operations and includes legal issues such as national and regional laws on quality standards, patent status and benefit sharing.

The safety and quality of raw medicinal plant materials and finished products depend on genetic or external factors, including environment, collection methods, cultivation, harvest, post-harvest processing, transport and storage practices. Inadvertent contamination by microbial or chemical agents during any of the production stages can also lead to deterioration in safety and quality. Medicinal plants collected in the wild may be contaminated by other species or plant parts through misidentification, accidental contamination or intentional adulteration, all of which may have unsafe consequences. Examples of this are:

Digitalis: Cases of serious cardiac arrhythmias were reported in the USA in 1997 following the accidental substitution of plantain as a dietary supplement with *Digitalis lanata*, generally used for heart conditions. Subsequent investigations revealed that large quantities of mislabelled plantain had been shipped to more than 150 manufacturers, distributors and retailers over a two-year period.

Podophyllum: Fourteen cases of *Podophyllum* poisoning were reported from Hong Kong, China following the inadvertent use of *Podophyllum hexandrum* root instead of *Gentiana* and *Clematis* species, for their antiviral qualities. This accidental substitution arose through the apparent similarity in morphology of the root.

Aconitum: Cases of cardiotoxicity resulting from the ingestion of *Aconitum* species used in complementary medicine for acute infections and panic attacks have been reported. *Aconitum* rootstocks are processed by soaking or boiling in water to hydrolyse the aconite alkaloids into a less toxic, aconine derivative. Toxicity can result when such processes are mismanaged. In the United Kingdom, the internal use of aconite is restricted to prescription only.

Endangered medicinal plants

The wild type of ginseng (*Panax ginseng*), used to address digestive conditions resulting from nervous disorders, is currently reported to be rapidly declining due to increasing demand and collection. While wild American ginseng, goldenseal, echinacea, black cohosh, slippery elm and kava kava top the “at-risk list” of endangered species of medicinal plants.

Cultivation has replaced wild collection for the supply of some essential drugs used in modern medicine. The Madagascar rosy periwinkle, *Catharanthus roseus*, is widely cultivated in Spain and the United States for its properties for treating childhood leukaemia and Hodgkin disease.

Demand is also greater than supply for the bark of Pygeum (*Prunus africana*), a popular natural remedy for prostate disorders in European countries which is harvested from wild trees growing in the mountain forests of continental Africa and Madagascar. Demand is currently unsustainable.

Devil’s Claw (*Harpagophytum procumbens*) is also unsustainably harvested and may become extinct in the wild under current practices. It is used as a tonic, treatment for arthritis and rheumatism, to reduce fever, ease sore muscles, reduce cholesterol, and externally the ointment is used to treat sores, boils, and ulcers. It is also used to cleanse the lymphatic system, and to remove toxins from the blood.

Reference: WHO Note for the Press No. 3,10 February 2004

Regulatory and Safety Action

Nevirapine and hepatotoxicity

Canada — The manufacturer of nevirapine (Viramune®) has provided new safety information clarifying risk factors for severe, life-threatening and fatal hepatotoxicity. Nevirapine, a non-nucleoside reverse transcriptase inhibitor, is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

New labelling information is being added concerning 200 mg tablets.

Women with CD4 counts >250 cells/mm^3 at initiation of therapy, including pregnant women receiving chronic treatment for HIV infection, are at considerably higher risk (12–fold) of hepatotoxicity, which in some cases has been fatal. This subset of patients was identified by analyses of CD4 count at the time of initiation of therapy.

The greatest risk of severe and potentially fatal hepatic events (often associated with rash) occurs in the first 6 weeks of treatment. However, the risk continues after this time and patients should be closely monitored for the first 18 weeks of treatment. In some cases, hepatic injury progresses despite discontinuation of the drug.

This new information is the result of recent post-marketing surveillance data. Although this new information describes patients at increased risk, it is important to note that any patient can experience hepatic events and should be monitored carefully. It may be prudent initially to conduct clinical and laboratory monitoring more often than once per month, for example, liver function tests at baseline, prior to dose escalation and at two weeks post dose escalation.

All patients developing a rash, at any time during treatment, but particularly during the first 18 weeks, should have liver function tests performed at that time. After the initial 18 week period, frequent clinical and laboratory monitoring should continue throughout treatment. Patients with rash and moderate to severe elevations should be permanently discontinued from nevirapine and in any patient experiencing constitutional symptoms, hepatitis, severe skin reactions or hypersensitivity reactions.

Stevens-Johnson Syndrome and toxic epidermal necrolysis may be preceded by a prodrome of flu-like symptoms including fever, malaise, rhinitis, nausea, chest pain, vomiting, sore throat, cough, dizziness, diarrhoea, headache, myalgia and arthralgia. Patients should be closely monitored if flu-like symptoms and/or an isolated rash occurs.

Based upon Canadian post-marketing data, since 1998, there has been one reported case of life threatening Stevens-Johnson Syndrome with hepatitis (non fatal) in a woman treated with Viramune® in combination with other antiretroviral agents.

Reference: Important Safety Information on nevirapine. 20 February 2004. http://www.

Antidepressants in adults and children

United States of America — The Food and Drug Administration (FDA) has cautioned health care professionals and patients about the need to closely monitor adults and children treated for depression following reports suggesting an increased risk of suicidal thoughts and actions in children given antidepressants.

FDA has initiated a full review and it is not yet clear whether antidepressants contribute to the emergence of suicidal thinking and behaviour. In the meantime, the agency is advising clinicians, patients, families and caregivers of adults and children that they should closely monitor all patients being placed on therapy with these drugs for worsening depression and suicidal thinking, which can occur during the early period of treatment.

The agency is also advising that these patients be observed for certain behaviours that are known to be associated with these drugs, such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restless-

ness), hypomania, and mania, and that physicians be particularly vigilant in patients who may have bipolar disorder.

The manufacturers of ten drugs will include stronger cautions and warnings about the need to monitor patients for the worsening of depression and the emergence of suicidal ideation, regardless of the cause of such worsening. The drugs under review include bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram and venlafaxine.

The only drug that has received approval for use in children with major depressive disorder is fluoxetine (Prozac®). Several of these drugs are approved for the treatment of obsessive-compulsive disorder in paediatric patients, i.e., sertraline (Zoloft®), fluoxetine (Prozac®), and fluvoxamine (Luvox®). Fluvoxamine is not approved as an antidepressant in the United States.

Reference: *FDA Talk paper*, T04-08. 22 March 2004.

Recommended influenza vaccines: 2004–2005

World Health Organization — The composition of influenza vaccines for the Northern hemisphere 2004–2005 Winter season has been determined as follows:

- an A/New Caledonia/20/99(H1N1)-like virus
- an A/Fjian/411/2002(H3N2)-like virus. (The currently used vaccine virus is A/Wyoming/3/2003 A/Kumamoto/102/2002 is also available.)
- a B/Shanghai/361/2002-like virus. (Candidate vaccine viruses include B/Shanghai/361/2002 and B/Jilin/20/2003.)

The national control authorities should approve the specific vaccine viruses used in each country. National public health authorities are responsible for recommendations regarding use of the vaccine. Updated epidemiological information is available on WHO's website at http://who.int/influenza.

Reference: *Weekly Epidemiological Record*, **79**: 91 (2004)

Olanzapine and cerebrovascular events

Canada — The manufacturer of olanzapine (Zyprexa®) has circulated information pertaining to cerebrovascular adverse events that have occurred in elderly patients with dementia-related psychosis treated with olanzapine in clinical trials. Olanzapine is not approved for use in elderly patients with dementia-related psychosis.

Recent analysis of some clinical trials in elderly patients with dementia suggests that the use of olanzapine in these patients may be associated with an increased incidence of cerebrovascular adverse events (CVAEs) such as stroke and transient ischemic attacks, including few fatalities.

While elderly patients are at increased risk of CVAEs, the above clinical trial data reflect an increased incidence of such adverse events in patients taking olanzapine compared with placebo-treated dementia patients after adjusting for age, gender, and type of dementia.

Physicians should counsel their patients/caregivers to immediately report signs and symptoms of potential CVAEs such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems, so that diagnosis can be made and treatment options considered, including discontinuation, without delay.

The current prescribing information states that olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolaemia, and treatment with antihypertensive medications).

Reference: Health Canada, http://www.hc-sc.gc.ca10 March 2004.

Olanzapine: hyperglycaemia and diabetes

United States of America — The Food and Drug Administration (FDA) has asked all manufacturers of atypical antipsychotic medications to add a warning statement describing the increased risk

of hyperglycaemia and diabetes. The atypical antipsychotic class includes olanzapine, clozapine, risperidone, quetiapine, ziprasidone, , and aripiprazole.

The manufacturer of olanzapine (Zyprexa®) has updated prescribing information as follows.

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Reference: http://www.fda.gov/medwatch. 1 March 2004.

Better labelling for ingredient sensitivities

United States of America —The Food and Drug Administration (FDA) has published new rules on content labeling (amount present per dosage unit) and warning labeling for over-the-counter (OTC) drugs that contain levels of calcium, magnesium, sodium, or potassium that might be harmful to people with certain underlying medical conditions. The rules require uniform content and warning labeling for oral OTC drug products containing levels of these substances that exceed specific thresholds. In addition, the agency is proposing to extend sodium content labeling requirements to OTC rectal drug products containing sodium phosphates. FDA is taking this action because people with certain medical conditions may be at risk for serious or life-threatening electrolyte imbalances when using these products.

Under the new rules, the labeling of oral OTC drugs containing sodium, calcium, magnesium, or potassium must state the amount of a particular ingredient in each dose if they contain:

- 5 milligrams (mg) or more of sodium in a single dose;
- 20 mg or more of calcium in a single dose;
- 8 mg or more of magnesium in a single dose; or
- 5 mg or more of potassium in a single dose.

The new rules also require new warnings on the label to alert people with kidney stones, decreased kidney function due to kidney disease, or people who are on sodium, calcium, magnesium, or potassium-restricted diets to consult their doctors before using products for oral ingestion that contain:

- more than 140 mg of sodium as the maximum daily dose.
- more than 3.2 grams of calcium as the maximum daily dose,
- more than 600 mg of magnesium as the maximum daily dose, or
- more than 975 mg potassium as the maximum daily dose.

Sodium may be related to high blood pressure and is a concern for individuals with congestive heart failure. In people with kidney disease, blood levels of calcium, magnesium, and potassium can reach potentially dangerous levels due to their decreased elimination. People with kidney stones need to carefully monitor their calcium intake.

Reference: *FDA News*, P04-35 25 March 2004

Consultation Document

The International Pharmacopoeia — monographs for antiretrovirals

Within the framework of the Pilot Procurement Project for Quality and Sourcing of HIV Drugs (http://www.who.int/medicines), the International Pharmacopoeia is collaborating with manufacturers, independent analytical drug quality control laboratories, national and regional pharmacopoeial bodies, research, governments, and regulatory bodies to provide specifications and monographs for the following antiretroviral agents:

abacavir, didanosine, efavirenz, indinavir, lamivudine, nelfinavir, nevirapine, ritonavir, saquinavir, stavudine, zidovudine

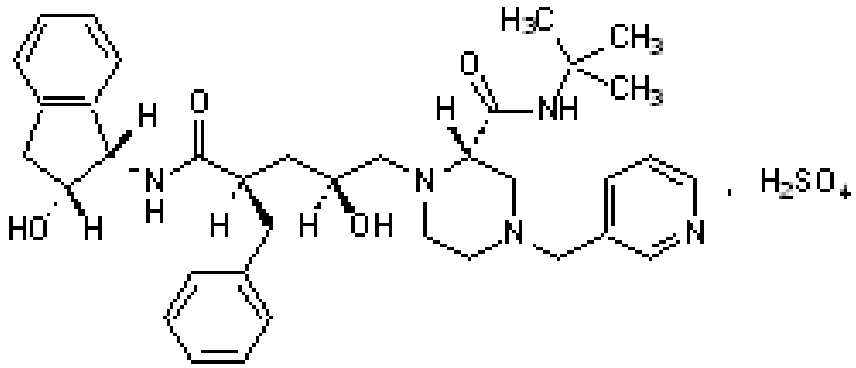
Specifications for the respective dosage forms will be developed during a second phase of the project. The draft monographs, Indinavir sulfate, nelfinavir mesilate, and nevirapine are now available for consultation and are presented below. Comments should be sent to: Quality and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland or kopps@who.int.

Indinaviri sulfas
Indinavir sulfate

Molecular formula: $C_{36}H_{49}N_5O_8S$ or $C_{36}H_{47}N_5O_4,H_2O_4S$

Relative molecular mass. 711.9

Graphic formula:



Chemical name: (2*S*)-1-[(2*S*,4*R*)-4-benzyl-2-hydroxy-5-[[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]amino]-5-oxopentyl]-*N*-(1,1-dimethylethyl)-4-(pyridin-3-ylmethyl)piperazine-2-carboxamide sulfate
CAS Reg. No. 157810-81-6

Description: White or almost white powder.

Solubility: Freely soluble in water, soluble in methanol.

Category: Antiretroviral (protease inhibitor).

Storage: Indinavir sulfate should be kept in a tightly closed container, protected from light.

Additional information: Indinavir sulfate is hygroscopic in nature and occurs as monoethanolate. Converts to hydrate upon loss of ethanol and exposure to moist air.

Requirements

Indinavir sulfate contains not less than 98.5% and not more than 101.0 % of $C_{36}H_{47}N_5O_4.H_2SO_4$ calculated on anhydrous, ethanol free basis.

Identity tests

Either tests A and B, or test C alone may be applied.

A. TLC: to be added.

B. The absorption spectrum of a 0.100 mg/ml solution in water, when observed between 220 nm and 280 nm, exhibits one maximum at about 260 nm; the specific absorbance ($A^{1\%}_{1cm}$) is 56 to 62.

C. Carry out the examination as described under “Spectrophotometry in the infrared region” (Vol. 1, p. 40[1]). The infrared absorption spectrum is concordant with the reference spectrum of indinavir sulfate.

Specific optical rotation. Use a 10.0 mg/ml solution in water and calculate with reference to the anhydrous and ethanol free substance; $[\alpha]_D$ 20 °C = +27° to +31°.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under “Limit test for heavy metals”, Procedure 1 (Vol. 1, p. 118[1]); determine the heavy metals content according to method A (Vol. 1, p. 118[1]); not more than 10 μg/g.

Sulfated ash. Not more than 1.0 mg/g (Vol. 1, p. 123[1]).

Water. Determine as described under “Determination of water by the Karl Fischer method”, Method A (Vol. 1, p. 135[1]), using 0.5 g of the substance; the water content is not more than 15 mg/g.

pH value. pH of a 10 mg/ml solution in carbon dioxide free water R, 2.8-3.2.

Ethanol content. Determine by “Gas chromatography with static head-space injection”. Use a fused-silica capillary or wide bore column 30 m long and 0.32 mm or 0.53 mm in internal diameter coated with macrogol 20 000 R (film thickness: 0.25 μm).

As detector use a flame ionization detector.

Use nitrogen for chromatography R or helium for chromatography R as the carrier gas at an appropriate pressure and a split ratio 1:5 with a linear velocity of about 35 cm/sec.

[1] Refers to *The International Pharmacopoeia.*

The following head-space injection conditions may be used:

Equilibration temperature (°C)	80
Equilibration time (min)	60
Transfer line temperature (°C)	85
Pressurization time (s)	30
Injection volume (ml)	1

Maintain the temperature of the column at 30 °C for 10 min, then raise the temperature at a rate of 5 °C per min to 70 °C, then raise the temperature at a rate of 15 °C per min to 180 °C and maintain for 10 min, maintaining the temperature of the injection port at 140 °C and that of the flame ionization detector at 250 °C.

Test solution. Dissolve 0.200 g of indinavir sulfate in purified water and dilute to 20.0 ml with the same solvent. Introduce 5.0 ml of this solution and 1.0 ml of purified water into an injection vial.

Reference solutions. Add 0.200 g of ethanol R to purified water and dilute to 200.0 ml with the same solvent. Transfer respectively 2.0 ml, 3.0 ml and 4.0 ml in separate injection vials and bring the volume to 6.0 ml with purified water.

Blank solution: Introduce 6.0 ml of purified water into an injection vial.

Analyse the blank vial and then alternatively test vials and reference vials.

The test is not valid unless the relative standard deviation on the areas of the peaks obtained from the test vials is not more than 15%.

Calculate the ethanol content by using the results obtained with the test vials and with the reference vials; the ethanol content is not less than 50 mg/g and not more than 80 mg/g.

Related substances. Carry out the test as described under "High–performance liquid chromatography" (Vol. 5, p. 257[1]), using a stainless steel column (25 cm x 4.6 mm) packed with base-deactivated octadecylsilyl silica gel for chromatography R (5 μm).

Use the following conditions for gradient elution:

Mobile phase A: 30 volumes of acetonitrile, 5 volumes of phosphate buffer pH 7.5 and 65 volumes of purified water.

Mobile phase B: 70 volumes of acetonitrile, 5 volumes of phosphate buffer pH 7.5 and 25 volumes of purified water.

Prepare the phosphate buffer pH 7.5 by dissolving 1.4 g of disodium hydrogen phosphate in 50 ml of purified water, adjust the pH to 7.5 by adding phosphoric acid (105 g/l) and dilute it to 100 ml with purified water.

Time (min)	Mobile phase A (%)	Mobile phase B (%)	Comments
0-5	93	7	isocratic
5-25	93 to 20	7 to 80	linear gradient
25-30	20	80	isocratic
30-35	20 to 93	80 to 7	return to the initial conditions
35-45	93	7	isocratic re-equilibration

[1] Refers to *The International Pharmacopoeia*.

Prepare the following solutions. For solution (1) use 2.0 mg of Indinavir sulfate per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 2 μg of Indinavir sulfate per ml.

For the system suitability test: prepare solution (3) using 2 ml of solution (1) and 2 ml of sulfuric acid (190 g/l), heat in a water bath at 80 °C for 60 minutes.

Operate with a flow rate of 1 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Maintain the column at 40 °C.

Inject solution (3). The test is not valid unless the resolution factor between the principal peak and the peak which is coming after the principal peak is not less than 3.5. If necessary adjust the amount of acetonitrile in mobile phase A.

Inject alternatively 20 μl each of solution (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). In the chromatograms obtained with solution (1), the area of any peak, other than the principal peak, is not greater than that obtained with solution (2) (0.10 %). The sum of the areas of all peaks, other than the principal peak, is not greater than five times the area of the principal peak obtained with solution (2) (0.50 %). Disregard any peak with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with the solution (2) (0.02%).

Assay: Dissolve 0.30 g, accurately weighed, in 50 ml of water and titrate with sodium hydroxide (0.1 mol/l) VS, determine the end point potentiometrically. Each ml of sodium hydroxide (0.1 mol/l) VS is equivalent to 35.59 mg of $C_{36}H_{47}N_5O_4.H_2SO_4$; calculate with reference to the anhydrous and ethanol free substance.

Reagents

Silica gel for chromatography, octadecylsilyl, base deactivated
A very finely divided silica gel, pretreated before the bonding of octadecylsilyl groups to minimize the interaction with basic compounds.

Macrogol 20 000 R. Polyethyleneglycol 20 000
Description. White or almost white solid with a waxy or paraffin-like appearance.
Solubility. Very soluble in water and methylene chloride R. Practically insoluble in alcohol and in fatty oils and mineral oils.

Nitrogen for chromatography.
Contains not less than 99.95% V/V of N_2.

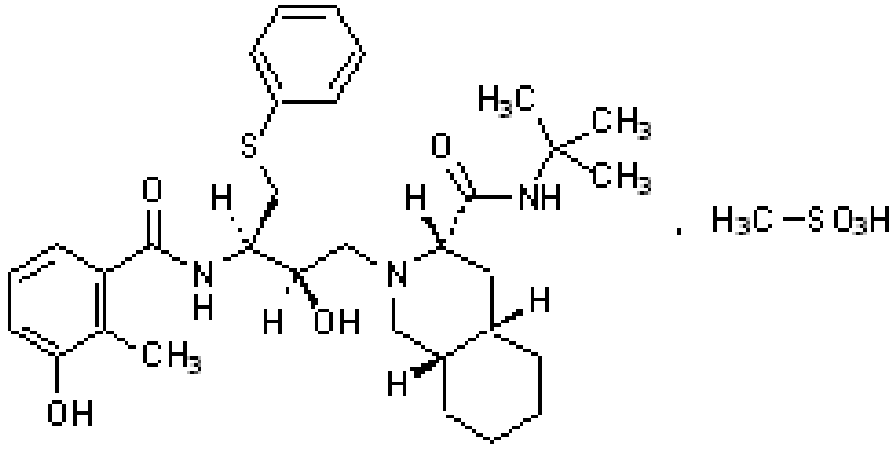
Helium for chromatography.
Contains not less than 99.995% V/V of He.

Nelfinavir mesilas
Nelfinavir mesilate

Molecular formula: $C_{32}H_{45}N_3O_4S,CH_4O_3S$

Relative molecular mass: 663.9

Graphic formula:



Chemical name: (3*S*,4a*S*,8a*S*)-*N*-(1,1-dimethylethyl)-2-[(2*R*,3*R*)-2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylsulfanyl)butyl]decahydroisoquinoline-3-carboxamide methanesulfonate
CAS Reg. No. 159989-65-8.

Description: White or almost white powder.

Solubility: Practically insoluble in water and soluble in methanol R.

Category: Antiretroviral (protease inhibitor).

Storage: Nelfinavir mesilate should be kept in a tightly closed container, protected from light.

Additional information: Nelfinavir mesilate is hygroscopic.

Requirements

General requirement: Nelfinavir mesilate contains not less than 98.0 % and not more than 101.0 % of $C_{32}H_{45}N_3O_4S.CH_4O_3S$, calculated with reference to the dried substance.

Identity tests

Either tests A and B or test C may be applied.

A. TLC: to be done.

B. The absorption spectrum of a 40 μg/ml solution in methanol R, when observed between 220 nm and 280 nm, exhibits one maximum at about 253 nm; the specific absorbance ($A^{1\%}_{1cm}$) calculated with reference to the dried substance is 124 to136.

C. Carry out the examination as described under “Spectrophotometry in the infrared region” (Vol. 1, p. 40[1]). The infrared absorption spectrum is concordant with the reference spectrum of nelfinavir mesilate.

Specific optical rotation: Use 10.0 mg/ml solution in methanol R and calculate with reference to the dried substance; $[\alpha]_D$ 20 °C = –110 ° to –125 °.

Heavy metals: Use 1.0 g in 30 ml of methanol R for the preparation of the test solution as described under “Limit test for heavy metals”, Procedure 2, (Vol. 1, p.118[1]); determine the heavy metals content according to method A (Vol. 1, p.118[1]); not more than 20 μg/g.

Sulfated ash: Not more than 1.0 mg/g. (Vol. 1, p.123[1]).

Loss on drying: Weigh 1.000 g, dry to constant mass at 100 °C; it loses not more than 30 mg/g.

Related substances: Carry out the test as described under “High–performance liquid chromatography” (Vol. 5, p. 257[1]), using a stainless steel column (25 cm x 4.6 mm) packed with base-deactivated octadecylsilyl silica gel for chromatography R (5μm) (Note: Hypersil BDS C18 is suitable.)

Use the following conditions for gradient elution:

Mobile phase A: 27 volumes of acetonitrile R, 20 volumes of methanol R, 28 volumes of phosphate buffer pH 3.4 and 25 volumes of purified water.

Mobile phase B: 41 volumes of acetonitrile R, 31 volumes of methanol R and 28 volumes of phosphate buffer pH 3.4.

Prepare the phosphate buffer pH 3.4 by dissolving 4.88 g of anhydrous sodium dihydrogenphosphate in 800 ml of purified water, adjust the pH to 3.4 by adding phosphoric acid (105 g/l) and dilute it to 1000 ml with purified water.

Time (min)	Mobile phase A (%)	Mobile phase B (%)	Comments
0–27	100	0	isocratic
27–60	100 – 0	0 – 100	linear gradient
60–75	0	100	isocratic
75–80	0 – 100	100 – 0	return to the initial conditions
80–90	100	0	isocratic re-equilibration

Prepare the following solutions using mobile phase A as diluent. For solution (1) use 2.0 mg of nelfinavir mesilate per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 10.0 μg of nelfinavir mesilate per ml. For solution (3) use 100 μg of methanesulfonic acid per ml.

For the system suitability test: prepare solution (4) using 2 ml of solution (1) and 5 ml of sulfuric acid (475 g/l), heat carefully in a water bath at 90 °C for 110 minutes.

Operate with a flow rate of 1 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 225 nm.

Maintain the column at 35 °C.

[1] Refers to *The International Pharmacopoeia.*

Inject 20 µl of solution (4). The test is not valid unless the resolution factor between the principal peak and the peak with a retention time relative to the principal peak of about 0.2 is not less than 15. The test is also not valid unless the resolution factor between the last two peaks out of three peaks, which are growing during decomposition, is not less than 4.0. The ratio of the retention times of these two peaks relative to the principal peak is about 1.8 and 1.9 respectively. If necessary adjust the amount of acetonitrile in both mobile phases A and B.

Inject 20 µl of solution (3).

Inject alternatively 20 µl each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the content of related substances as a percentage. In the chromatograms obtained with solution (1), the area of any peak, other than the principal peak, is not greater than that obtained with solution (2) (0.5 %). The sum of the areas of all peaks, other than the principal peak, is not greater than two times the area of the principal peak obtained with solution (2) (1.0 %). Disregard any peak with an area less than 0.04 times the area of the principal peak in the chromatogram obtained with solution (2) (0.02%). Ignore any peak due to methanesulfonic acid, corresponding to the principal peak in the chromatogram obtained with solution (3).

Assay: Dissolve about 0.50 g, accurately weighed, in 50 ml of methanol R and titrate with sodium hydroxide (0.1 mol/l) VS, determine the end point potentiometrically. Perform a blank determination and make the necessary correction. Each ml of sodium hydroxide (0.1 mol/l) VS is equivalent to 66.39 mg of $C_{32}H_{45}N_3O_4S.CH_3SO_3H$.

Reagents

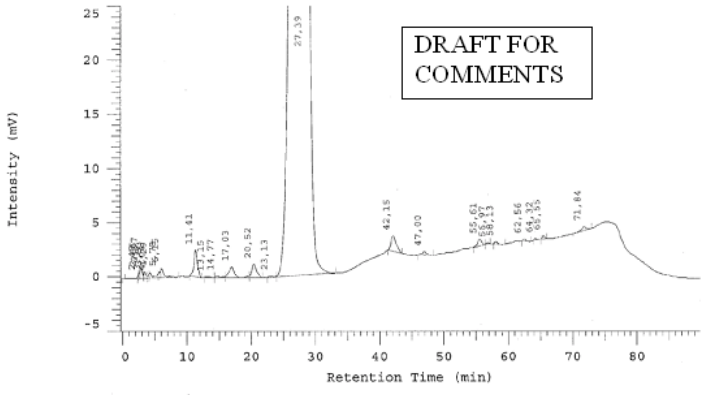
Silica gel for chromatography, octadecylsilyl, base-deactivated

A very finely divided silica gel, pre-treated before the bonding of octadecylsilyl groups to minimize the interaction with basic compounds.

Methanesulfonic acid R

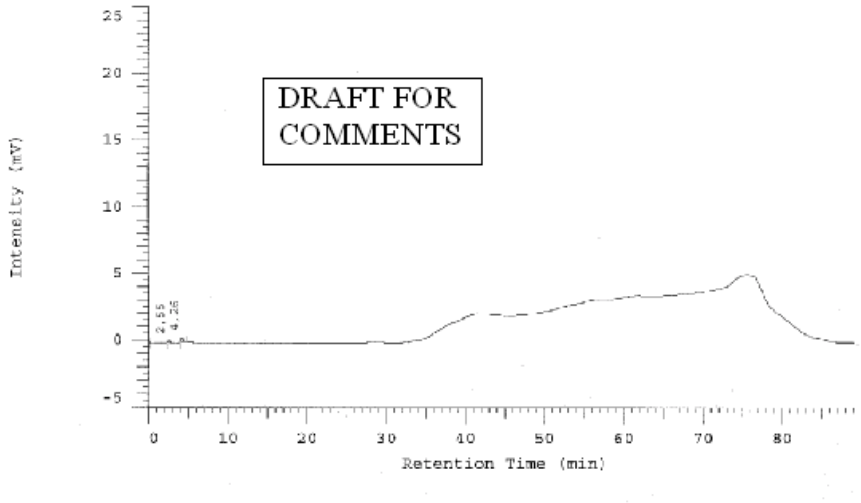
Molecular formula. CH_4O_3S
Description. Colourless and corrosive liquid.
Solubility. Miscible with water.
Density (d). ~1.48.
Melting point. About 20 °C.

A typical chromatogram obtained for nelfinavir mesilate (Refer to the monograph text for chromatographic conditions in “Related substances” [1])

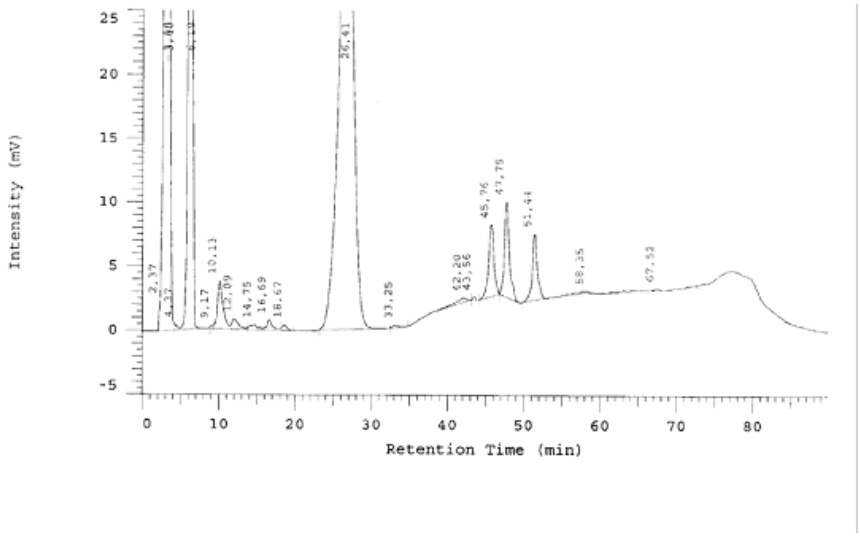


[1] Refers to *The International Pharmacopoeia.*

A typical chromatogram obtained for blank (Refer to the monograph text for chromatographic conditions in “Related substances”)



A typical chromatogram obtained for system suitability (Refer to the monograph text for system suitability conditions in “Related substances”)

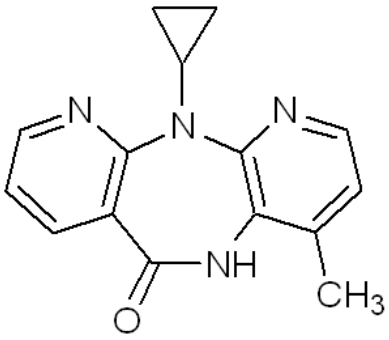


Nevirapinum anhydricum
Nevirapine anhydrous

Molecular formula: $C_{15}H_{14}N_4O$

Relative molecular mass: 266.30

Graphic formula:



Chemical name: 11-cyclopropyl-4-methyl-5,11-dihydro-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one
CAS Reg. No. 129618-40-2.

Description: White to almost white powder.

Solubility: Very slightly soluble in water and soluble in acidic solution.

Melting point: 242 – 246 °C.

Category: Antiretroviral (non-nucleoside reverse transcriptase inhibitor).

Storage: Nevirapine should be kept in a well closed container.

Requirements

Nevirapine contains not less than 99.0 % and not more than 101.0 % of $C_{15}H_{14}N_4O$, calculated with reference to the dried substance.

Identity test
Carry out the examination as described under "Spectrophotometry in the infrared region" (Vol. 1, p. 40[1]). The infrared absorption spectrum is concordant with the spectrum obtained from nevirapine RS.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry for 4 hours at 105 °C; it loses not more than 10 mg/g.

[1] Refers to *The International Pharmacopoeia.*

Related Substances

Note: Prepare fresh solutions and perform the tests without delay

Carry out the test as described under "High-performance liquid chromatography" (Vol. 5, p. 257[1]), using a stainless steel column (15cm x 4.6mm), packed with hexadecylamidylsilyl silica gel for chromatography (5 μm). (Supelcosil LC-ABZ is suitable.)

Maintain the column temperature at 35 °C.

The mobile phase consists of a filtered and degassed mixture of 20 volumes of acetonitrile R and 80 volumes of a buffer of 25 mM ammonium dihydrogen phosphate adjusted to pH 5.0 using a 20 % w/w ammonia solution.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 220 nm.

Prepare the following solutions in the mobile phase (dissolution solvent).
For solution (1) dissolve 25 mg of nevirapine in 4 ml of acetonitrile R and dilute to 100.0 ml with the dissolution solvent. For solution (2) dilute 5.0 ml of solution (1) to 50.0 ml with the dissolution solvent. Then dilute 5.0 ml of this solution to 50.0 ml with the same solvent.

Inject separately 50 μl of solution (2) in replicate injections in the chromatographic system. The relative standard deviation for peak areas of Nevirapine in replicate injections of solution (2) is not more than 5.0%.

Inject separately 50 μl each of solution (1) and of mobile phase in the chromatographic system. Continue the chromatography for 5 times the retention time of nevirapine. Examine the mobile phase chromatogram for any extraneous peaks and disregard the corresponding peaks observed in the chromatogram obtained with solution (1).

The test is not valid unless the column efficiency determined from the solution (2) is not less than 10000. The peak symmetry should be between 0.8 and 1.2 .

In the chromatogram obtained with solution (1), the following impurity peaks are eluted at the following relative retention time with reference to nevirapine: (A) = about 0.7; (B) = about 1.5 and (C) = about 2.8.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the content of related substances as a percentage.

In the chromatogram obtained with solution (1) the area of any individual peaks corresponding to impurity peaks A, B and C is not greater than 0.2 times the area of the principal peak obtained with solution (2) (0.2%). Any other impurity peak is not greater than 0.1 times the area of the principal peak obtained with solution (2) (0.1%). The sum of the areas of all peaks, other than the principal peak, is not greater than the area of the principal peak obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (2) (0.05%).

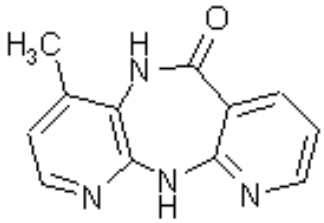
Assay

Dissolve about 0.200 g, accurately weighed, in 50 ml of acetic anhydride R and titrate with perchloric acid (0.1 mol/l) VS as described under "Non-aqueous titration"; Method A (Vol. 1, p.131[1]) determining the end point potentiometrically.

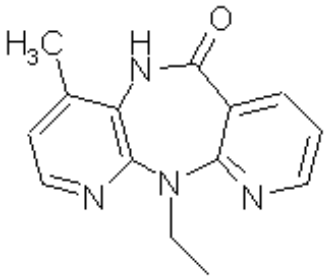
[1] Refers to *The International Pharmacopoeia.*

Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 26.63 mg of $C_{15}H_{14}N_4O$.

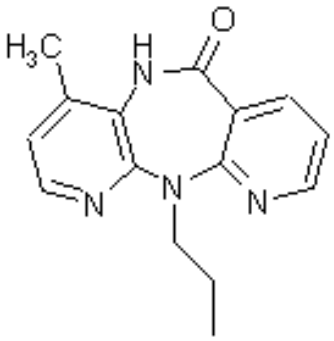
Tested impurities



A. 5,11-Dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one



B. 11-Ethyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one



C. 11-Propyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one

Reagents

Silica gel for chromatography, hexadecylamidylsilyl
Particles of silica gel, the surface of which has been modified with chemically bonded hexadecylamidylsilyl groups.

[1] Refers to *The International Pharmacopoeia.*