Regulatory harmonization
297 16th International Conference of Drug Regulatory Authorities (ICDRA)
298 16th ICDRA recommendations

WHO Prequalification
307 Ensuring global availability of quality-assured vaccines
312 Bringing quality-assured in vitro diagnostics to WHO Member States

Medicines quality
317 Combating unsafe medical products: outcomes of a survey on testing of suspect medicines

Safety news
324 Unchanged recommendations
Olmesartan in diabetic patients
• Levonorgestrel and ulipristal emergency contraceptives
324 Restricted use
Bromocriptine • Ferumoxytol • Intravenous ondansetron • Influenza vaccine (Fluvax®)
• Etonogestrel / ethinyl estradiol vaginal ring
326 Safety warnings
Lidocaine oral viscous solution • Terconazole cream • Docetaxel • Topical acne products
• Testosterone • Paracetamol • Ofatumumab
• Fentanyl patches • Sugammadex • Interferon beta products • Topiramate
329 Suspended
Methadone with high molecular weight povidone
330 Overview of safety reviews started

Regulatory news
332 Data-sharing
EMA Board agrees on clinical trial data-sharing policy • Canada advances transparency legislation • FDA launches public data access platform
333 Generics
Generic registration information-sharing pilot launched
333 Regulatory oversight
Canada implements labelling changes for opioids, adopts plain language labelling regulations • FDA outlines expectations for medicines compounding • FDA proposes new guidance for certain types of diagnostics
334 Orphan medicines
Canada pilot project seeks patient perspectives on orphan medicines
335 Submitted for approval
Malaria vaccine
335 Approved
Inhaled insulin (human) • Eliglustat
• Recombinant antihaemophilic factor • Daclatasvir • Dolutegravir / abacavir / lamivudine fixed-dose combination • Tedizolid phosphate • Oritavancin • Belinostat • Ibrutinib
• Idelalisib • Bevacizumab • Suvorexant • Olodaterol • Technetium 99m tilmanocept • Flutemetamol (¹⁸F)
338 Withdrawn applications

Publications and events
339 Emergency
WHO panels advise on medical interventions in Ebola outbreak
340 Public health
UNAIDS report on HIV treatment coverage • Access to antiretroviral medicines in low- and middle-income countries • UK studies show safety and effectiveness of whooping cough vaccination in pregnant women
341 Organizations
Swissmedic and Health Canada join ICH Steering Committee • Novartis transfers tuberculosis drug development to Global TB Alliance

341 WHO matters
Why we need an independent, impartial WHO • The International Pharmacopoeia – Fourth Supplement published • WHO-ISoP core elements of teaching pharmacovigilance

Consultation documents
343 Medicines quality assurance texts
343 General guidance on “hold-time” studies
348 Good review practices guidelines for regulatory authorities

349 The International Pharmacopoeia
349 Pyrantel embonate
353 Pyrantel tablets
356 Pyrantel chewable tablets
360 Dexamethasone sodium phosphate
366 Dexamethasone phosphate injection
370 Atazanavir sulfate
373 Atazanavir capsules
376 Albendazole chewable tablets

International Nonproprietary Names
379 Recommended List No. 72

Abbreviations and web sites
CHMP Committee for Medicinal Products for Human Use (EMA)
EMA European Medicines Agency (www.ema.europa.eu)
EU European Union
FDA U.S. Food and Drug Administration (www.fda.gov)
Health Canada Federal department responsible for health product regulation in Canada (www.hc-sc.gc.ca)
MHRA Medicines and Healthcare Products Regulatory Agency, United Kingdom (www.mhra.gov.uk)
Medsafe New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz)
PRAC Pharmacovigilance Risk Assessment Committee (EMA)
PMDA Pharmaceutical and Medical Devices Agency, Japan (www.pmda.go.jp/english/index.htm)
Swissmedic Swiss Agency for Therapeutic Products (www.swissmedic.ch)
TGA Therapeutic Goods Administration, Australia (www.tga.gov.au)
U.S. United States of America
UN United Nations

Note:
The online version of this issue, available at www.who.int/medicines/publications/druginformation, has direct clickable hyperlinks (in italic font) to the documents and web pages referenced.
Regulatory harmonization

16th International Conference of Drug Regulatory Authorities (ICDRA)

The 16th International Conference of Drug Regulatory Authorities (ICDRA) was held in Rio de Janeiro, Brazil, on 26–29 August 2014. The conference was hosted by the Brazilian Health Surveillance Agency ANVISA, in collaboration with WHO. The recommendations are set out on the following pages.

Government officials and regulators from more than 100 WHO Member States came together at this year’s ICDRA to discuss current challenges and strengthen collaboration. The ICDRA conferences, held every two years, have become a well-established forum for regulatory authorities, WHO and interested stakeholders to determine priorities for action in regulation of medical products.

A pre-conference titled “Ensuring Quality and Safety of Biosimilars for Patients Worldwide” was held on 24–25 August at the same venue. The ICDRA pre-conferences are open to participants from regulatory authorities, industry, academia and non-governmental and international organizations.

► WHO. International Conference of Drug Regulatory Authorities [web site]: http://www.who.int/medicines/icdra (includes links to recommendations and presentations of past ICDRA conferences)

► 16th ICDRA official web site: http://www.icdra.com.br

16th ICDRA sessions (recommendations, see pages 298–306)

<table>
<thead>
<tr>
<th>Session</th>
<th>Title</th>
<th>Page(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plenary 3</td>
<td>The role of drug regulatory authorities in national health systems</td>
<td>(p. 298)</td>
</tr>
<tr>
<td>Plenary 4</td>
<td>Strengthening regulatory systems for medical products</td>
<td>(p. 298)</td>
</tr>
<tr>
<td>Workshop A</td>
<td>Best practices in pharmacovigilance</td>
<td>(p. 299)</td>
</tr>
<tr>
<td>Workshop B</td>
<td>How to ensure the safety of traditional and complementary medicines in national healthcare systems</td>
<td>(p. 299)</td>
</tr>
<tr>
<td>Workshop C</td>
<td>Regulatory models for minimizing risks in blood and blood products</td>
<td>(p. 300)</td>
</tr>
<tr>
<td>Workshop D</td>
<td>Approaches to educating regulators to meet country needs</td>
<td>(p. 300)</td>
</tr>
<tr>
<td>Plenary 5</td>
<td>Regulators’ role in access/availability (shortages etc.)</td>
<td>(p. 300–301)</td>
</tr>
<tr>
<td>Plenary 6</td>
<td>New trends in regulating medical devices</td>
<td>(p. 301)</td>
</tr>
<tr>
<td>Workshop E</td>
<td>Challenges of vaccine safety regulation and safety monitoring</td>
<td>(p. 301)</td>
</tr>
<tr>
<td>Workshop F</td>
<td>Collaboration for ensuring the quality and safety of active pharmaceutical ingredients (APIs)</td>
<td>(pp. 301–302)</td>
</tr>
<tr>
<td>Workshop G</td>
<td>Preventing and reducing the risk to public health from substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products</td>
<td>(pp. 302–303)</td>
</tr>
<tr>
<td>Workshop H</td>
<td>Biosimilars</td>
<td>(pp. 303–305)</td>
</tr>
<tr>
<td>Workshop I</td>
<td>Current status and future vision of regulating advanced therapies</td>
<td>(pp. 305)</td>
</tr>
<tr>
<td>Workshop J</td>
<td>Managing decentralized Good Manufacturing Practice (GMP) systems</td>
<td>(p. 305)</td>
</tr>
<tr>
<td>Workshop K</td>
<td>Current challenges and transparency in clinical trials regulation</td>
<td>(pp. 305–306)</td>
</tr>
<tr>
<td>Workshop L</td>
<td>Current topics and future developments</td>
<td>(p. 306)</td>
</tr>
</tbody>
</table>
16th ICDRA recommendations

**Plenary 3**
The role of drug regulatory authorities in national health systems

- Strengthen the role of national regulatory authorities (NRAs) in public health protection and promotion, establishing the necessary governance and legal frameworks that will support NRAs in the exercise of this role, and establishing mechanisms to ensure effective linkages within the health, science/technology and industrial sectors, and with civil society, in order to contribute to universal health coverage.

- Strengthen the capacity of NRAs to assess and monitor the quality, safety and efficacy of medicines and medical products, ensuring effective implementation of core regulatory functions to support product registration and market authorization, as well as post-marketing surveillance, to monitor the use of the products in health services and during the complete product life cycle.

- Recognize the role of the NRA in supporting innovation and ensuring access to medical products in health systems and services by supporting regulatory processes that result in the introduction of safe new innovative medical products within health services, that guide the safe use of medical products in public health emergencies, and – in collaboration with other stakeholders – address shortages of essential medicines.

**Plenary 4**
Strengthening regulatory systems for medical products

- Recognize that effective regulatory systems are an essential component of health system strengthening that contribute to better public health outcomes; that regulators are an essential part of the health workforce; and that inefficient regulatory systems themselves can be a barrier to access safe, effective and quality medical products.

- Strengthen WHO’s role in strengthening regulatory systems for medical products from a public health perspective, and in supporting national drug regulatory authorities and relevant regional bodies in this area, and in particular in developing countries.

- Support the development and strengthening of national regulatory systems through the assessment of regulatory functions and system performance with WHO support, and the development and implementation of institutional development plans that will protect and promote health at the national level, and will pool and leverage regulatory capacity regionally and globally to promote access to quality, safe and efficacious and affordable medical products.

- Promote the greater participation of national regulatory authorities in existing international and regional initiatives and networks for collaboration and cooperation in accordance with WHO principles and guidelines, and increase support for and recognition of the significant role of the International Conference of Drug Regulatory Authorities in promoting the exchange of information and collaborative approaches among drug regulatory authorities, and as a resource to facilitate further development of regulatory cooperation and coherence.
Workshop A
Best practices in pharmacovigilance

Member States
- Implement Pharmacovigilance (PV) as an integrated service that informs and improves health-systems, health resources and health-care delivery;
- integrate PV within a regulatory framework to ensure accountability and best practices in the way medicinal products are handled throughout their life cycle;
- embrace robust tools and methods for risk-based PV, to collect, manage and exploit PV information, including the detection of irrational use and quality-related aspects;
- engage all relevant stakeholders (patients, industry, authority, academia, health professionals and others) to develop and implement comprehensive PV plans; and
- in order to participate in a global PV community, be the beneficiary and the benefactor of PV information.

WHO
- Promote PV as an overarching integrated service that informs public health programmes and supports regulatory decisions;
- maintain and convene the global PV network and database, and support the global exchange of PV information across Member States;
- facilitate PV convergence and alignment across Member States, to allow consistent and comparable PV practices, optimal information exchange and learning; and
- develop and support the adoption of international norms, standards and tools to promote risk-based PV and for the full scope of PV (irrational use, medication errors, quality-related aspects).

Workshop B
How to ensure the safety of traditional and complementary medicines in national healthcare systems

Member States
- Establish, strengthen and implement an effective regulation of providers of herbal medicines in respect of their qualification, in order to ensure the safety and quality of their practices;
- establish, strengthen and effectively enforce regulations on herbal medicines;
- strengthen capacity-building efforts for providers, manufactures and regulators of herbal medicines in order to improve their capacity and expertise regarding assurance of safety and quality of herbal medicines; and
- include safety monitoring on herbal medicines in pharmacovigilance systems and promote the awareness of consumers/patients on safety aspects of herbal medicines.

WHO
- Provide technical support to Member States in the implementation of the latest World Health Assembly resolution on traditional medicine (WHA67.18) and the WHO Traditional Medicine Strategy: 2014-2023, in particular regarding the safety of herbal medicines and of traditional and complementary medicine practices.
- Continue to provide technical support to Member States in:
  - strengthening national capacity for regulation of herbal medicines in ensuring the safety and quality of herbal medicines; and
  - sharing information regarding the safety of herbal medicines through global networking and relevant tools, including the networks of the International Regulatory Cooperation for Herbal Medicines (IRCH) and of the National Centres participating in the WHO International Drug Monitoring Programme.
Workshop C

Regulatory models for minimizing risks in blood and blood products

Member States

• Member States are encouraged to add whole blood and blood components (red blood cells, platelets and fresh frozen plasma) to their national lists of essential medicines consistent with their inclusion in 2013 on the WHO Model List of Essential Medicines.

• Member States are encouraged to establish regulation of whole blood and blood components on the model of biological therapeutics*1 in order to:
  – protect the health and safety of blood donors; and
  – assure the quality, safety, efficacy and availability of blood for transfusion, and of plasma for further manufacturing to make essential derivatives.

• Member States are encouraged to establish regulation of whole blood, blood components and plasma derivatives within the national regulatory authority, including:
  – appropriate risk-based selection and quality assurance of test kits for donor screening; and
  – assuring bidirectional traceability of blood components between donors and patients as a foundation of haemovigilance.

• Member States are encouraged to adopt internationally recognized standards for blood collection and processing as an essential element of blood regulation.

• National standards for blood collection, processing and testing should be established and enforced by the national regulatory authority.

WHO

• At the request of Member States, WHO should provide assistance on:
  – capacity-building for national blood systems including a national regulatory authority;

  – establishment of appropriate legal frameworks for blood regulation and strategies for their implementation.

Workshop D

Approaches to educating regulators to meet country needs

WHO

• Expedite coordination, development and launching of a global regulatory science curriculum; and

• develop and publish an inventory of accredited training centers and other training initiatives including specific areas of competency.

Plenary 5

Regulators’ role in access/availability (shortages etc.)

Member States

• Explore the possibilities to promote convergence and harmonization of regulatory processes, and use joint and collaborative assessments as appropriate (with neighbouring countries or between authorities with common interest in certain products), in order to facilitate registration of medical products and increase efficiency.

• Design and implement fast-track and/or abbreviated registration processes for medical products that have already undergone rigorous evaluation in other countries e.g. by using the Collaborative procedure between national regulatory authorities in user countries and the WHO Prequalification programme for vaccines and medicines for priority diseases.

• Share experiences in design of special procedures for registration of products in case of emergencies or structural shortages, and for parallel importation.

WHO and Member States

• WHO and countries should:
  – collaborate in setting up a global monitoring system on medicines shortages;

* The wording reflects recommendations as proposed and agreed during the conference; one comment was subsequently received.
– identify medicines vulnerable to supply interruption; and
– share experience in preventing and managing shortages.

► To respond to the Ebola virus disease (EVD) public health emergency of international concern, the following recommendations are made.

**Member States**
- Ensure there are emergency use regulatory pathways in place;
- ensure there is rapid and proactive cooperation and collaboration between regulators, and also with WHO, to help accelerate development and evaluation of investigational treatments and vaccines; and
- drive innovative clinical trial design for situations like the current EVD emergency where traditional clinical trial designs may not be feasible.

**WHO**
- Rapidly provide scientific information on the potential therapies and vaccines for EVD, and ensure the information is regularly updated;
- establish and lead a network of regulators globally to address the response to EVD; and
- facilitate collaborations between regulators in countries where products are being developed and those in countries where the products will be evaluated and, if found safe, used.

**Workshop E**
**Challenges of vaccine safety regulation and safety monitoring**

**Member States**
- Vaccine safety concerns need to be addressed on an individual basis, and regulatory action should be tailored to the clinical setting as well as to the safety issue, the disease, and the strength of the evidence available.
- A combined effort by national regulatory authorities to support WHO in setting appropriate monitoring systems for vaccines worldwide is encouraged, especially in relation to newer vaccines.

**WHO**
- Multi-country collaboration on surveillance and monitoring of vaccine safety concerns should be actively pursued, to maximize the use of resources and public health protection, under the WHO umbrella.
- WHO efforts to enhance maternal immunization efforts are commended and should continue with support from all stakeholders.

**Member States and WHO**
- Pharmacovigilance data from multiple sources should be considered, with special emphasis and continued efforts to harmonize reporting and collection of safety data.
- Efforts to raise the quality and quantity of relevant data on vaccines use during pregnancy should continue.

**Plenary 6**
**New trends in regulating medical devices**

**WHO**
- Continue and further strengthen international convergence/harmonization initiatives and normative work for medical devices, including IVDs, to support regulatory convergence in different jurisdictions.
- Support low- and middle-income countries (LMIC) to strengthen their regulations of medical devices, including IVDs, through provision of regulatory mechanisms that balance pre- and post-market regulatory oversight according to the risk level of the device.

**Workshop F**
**Collaboration for ensuring the quality and safety of active pharmaceutical ingredients (APIs)**

- At the request of Member States, WHO and Member States (well-resourced national regulatory authorities) should establish a system of targeted
capacity-building for ensuring the quality and safety of APIs:
- focusing on the needs and obligations of producing countries and user countries;
- emphasizing practical skills development through:
  ▪ twinning and staff placements;
  ▪ sustainable training approaches based on defined competencies (e.g., through a network of Centers of Excellence); and
  ▪ observed/collaborative/joint inspections.
- Member States should establish transparent regulatory systems, based on internationally agreed-upon standards, that will assure quality and safety of APIs produced and used in, and/or exported from their borders, ensuring that:
  - APIs and their intermediates are manufactured by regulated manufacturers; and
  - API suppliers and brokers are regulated.
- WHO and Member States should support and encourage the use of work-sharing mechanisms for ensuring the quality and safety of APIs, e.g. WHO Prequalification of APIs, Certificates of Suitability of the European Pharmacopoeia (CEP), the International Generic Drug Regulators Pilot (IGDRP), etc.
- WHO should facilitate establishment of guidance on good/risk-based regulatory practice, including identification and use of available regulatory expertise to facilitate local regulatory decisions.

Workshop G

Preventing and reducing the risk to public health from substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products

- With a view to reducing the risks to public health from SSFFC medical products, all Member States are strongly encouraged to:
  - participate in the WHO Member State Mechanism on SSFFC medical products, including implementation of the agreed work plan;
  - in particular, to participate in on line working groups both to:
    - establish recommendations to detect and deal with actions, activities and behaviours that result in SSFFC medical products, and
    - establish activities that fall outside of the mandate of the Member State Mechanism.
  - Within the framework of the Member State Mechanism, WHO should continue to provide support and build capacity in low-income countries to tackle SSFFC medical products.

- Prevention
  - National medicines regulatory authorities (NMRAs) are encouraged to develop a specific strategy to combat SSFFC medical products tailored to their national and regional needs, including but not restricted to:
    - targeted awareness campaigns for specific stakeholders; and
    - strengthening networks of key stakeholders to enable more effective collaboration, cooperation and communication.
  - NMRAs utilizing track, trace and authentication technologies should share knowledge and experience with a view to strengthening supply chain integrity.
WHO Drug Information Vol. 28, No. 3, 2014

16th ICDRA recommendations

- WHO and Member States should undertake research into the root causes of SSFFC medical products, including the scope, scale and harm caused to public health, health systems and Member States.

► Detection
- All NMRAs should have access to field testing equipment and/or Quality Control Laboratories;
- all NMRAs are encouraged to carry out risk-based post market surveillance and market surveys; and
- all NMRAs are encouraged to ensure sustainable pharmacovigilance reporting systems from healthcare professionals and the public, specifically including the lack of efficacy of a medical product.

► Response
- All NMRAs are encouraged to have developed procedures to respond to suspected SSFFC medical products, with particular attention to quarantine, seizure, sampling, analysis, recall, investigation, enforcement, information-sharing and collaborating with stakeholders.
- All NMRAs are encouraged to share information concerning incidents involving suspected SSFFC medical products with sub-regional and regional regulatory networks and WHO through rapid alert systems.
- In order to protect public health, all NMRAs should increase knowledge and understanding and influence evidence-based policy and resource allocation.

Workshop H
Biosimilars

1. Ensure regulatory oversight throughout the life cycle of biotherapeutic products, including similar biotherapeutic products, (SBP) to assure quality, efficacy and safety of these products

Member States
- Clearly define regulatory pathways for biotherapeutic products, including biosimilars, and make this information transparent and easily available (e.g. through a web site).
- Implement regulatory standards for approval of biological products that are aligned with WHO standards.
- Strengthen regulatory functions, in particular clinical evaluation and PV, including proactive collection of PV data.

WHO
- Update norms, standards, and tools to facilitate further development of expertise for regulatory evaluation of biologicals.
- Nomenclature for similar biotherapeutics is a complex issue for which there is no consensus yet; this is under discussion with the WHO INN Expert group, and a consultation with all Member States and stakeholders is under way.

2. Improve efficiency of regulatory evaluation of biotherapeutic products, including SBP, in order to improve access to products of assured quality, safety and efficacy

Member States
- Make effort to reduce time for evaluation without compromising quality of the review, in particular review time for the purpose of licensing or clinical trial approval.
- Facilitate the development and licensing of innovative molecules which could serve as reference products in the development of biosimilars.
- Develop information and/or work-sharing with other regulators for SBP (e.g.
recognition of other NMRAs' conclusions; work-sharing in sub-regional or regional networks).

WHO
• Continually update information regarding WHO standards for biologicals through regional and/or inter-regional networks and initiatives.

3. WHO guidelines on biotherapeutic products and on SBP

Member States
• Implement existing WHO guidelines and subsequent updates in full, and monitor levels of implementation over time.
• If national standards differ from WHO standards, inform WHO of the rationale for this situation.

WHO
• Amend Guidelines on evaluation of SBP by providing additional information on:
  – extrapolation of indication;
  – special considerations for evaluation of monoclonal antibodies;
  – acceptance criteria and evaluation of reference biotherapeutic products (RBP) including the reliance on reference agencies;
  – the design, conduct and interpretation of data for comparability exercise.
• Facilitate implementation of existing guidelines on SBP (adopted in 2009), and subsequent updates, and on biotherapeutic products made by recombinant DNA technology (adopted in 2013).
• Develop e-learning tools for different levels (e.g. basic, advanced).
• Prepare case studies for illustrating practical application of guiding principles to different scenarios, e.g. mimic the real situation.
• Make all materials from implementation workshop (i.e. lectures, discussions, and case studies) available to all regulators.
• Develop criteria and/or tool for assessing implementation level of WHO written standards (guidelines) into regulatory practice.

4. Collaboration between regulators and other relevant stakeholders

Member States
• Involve all relevant stakeholders (e.g. manufacturers, academia, health care providers, patient associations) during development of national regulatory requirements and create opportunities for regular feedback on regulatory practices.
• Develop national initiatives for better access to biotherapeutic products, including SBPs; such initiatives may include considerations on intellectual property issues, interchangeability, and substitutability. *
• Develop programmes to educate all relevant stakeholders on the nature and intended use of biosimilars, and define the role of each stakeholder in improving access to biotherapeutic products, including biosimilars. *

WHO
• Provide a forum for information-sharing on collaborative efforts that leads to better access.

5. Regulatory convergence as a tool to increase global access to SBPs of quality, safety, and efficacy

Member States
• Make effort to align national regulatory requirements with WHO guiding principles for biotherapeutic products, including SBP.
• Define terminology for naming SBP that enables clear identification of the evaluation pathway. *
• Use the term “biosimilar” for products that were demonstrated as similar through an evaluation that is in line with the biosimilar pathway as described in WHO Guidelines on evaluation of similar biotherapeutic products, only.

WHO
• Develop tools to measure progress in regulatory convergence.

* The three points marked with asterisks reflect recommendations as proposed and to which no objections were made at the time of adoption, but which do not necessarily represent consensus since some regulators expressed different views during the meeting.
Workshop I
Current status and future vision of regulating advanced therapies

- Products containing genetically modified viable cells should be considered cell therapy medicinal products. They are biological medicinal products.
- Products containing viable cells which are used in transfusion medicine (e.g. thrombocyte, erythrocyte, granulocyte concentrates) or for haematopoietic reconstitution are not considered cell therapy medicinal products.

Member States
- Member States are encouraged to develop regulatory expertise for cell therapy medicinal products appropriate for the specific nature of these products. In this regard it is recommended to:
  - share regulatory experiences among national regulatory authorities to allow appropriate regulatory responses; and
  - promote information-sharing between academia, industry and national regulatory authorities on newest technologies including stem cell therapies.
- Development of cell therapy medicinal products in clinical trials should be facilitated prior to standard clinical use after authorization by a national regulatory authority.
- Experimental product testing by the developer should be established and enforced by the national regulatory authority.

WHO
- WHO should consider developing guidance on manufacture, non-clinical and clinical aspects of cell therapy medicinal products, taking into account existing guidelines, points to consider and recommendations, with the collaboration of leading regulatory authorities.
- At the request of Member States, WHO should organize the provision of assistance on capacity-building for the regulation of cell therapy medicinal products.
- WHO should foster international collaboration between regulatory authorities regarding information-sharing to protect patients and the public from the risks of unauthorized cell therapy medicinal products.

Workshop J
Managing decentralized Good Manufacturing Practice (GMP) systems

- It is recommended that Member States, whatever their organizational model is in the field of GMP inspections, should ensure that all inspections are done in a consistent manner and that inter-inspector variability is measured and managed.
- It is recommended that Member States, when interacting with other Member States in the field of GMP inspections, make sure that any international inspection is notified well in advance to the national inspectorate on whose territory the inspection will take place, with the aim of allowing inspectors from that country to observe the inspection, thus serving the ultimate goal of creating mutual trust and recognition between inspectorates.

Workshop K
Current challenges and transparency in clinical trials regulation

Member States
- Increase the transparency of processes, and work towards consistency of approaches to transparency for clinical trial review and approvals across countries.
- Increase collaboration and cooperation to build capacity of regulatory authorities for oversight of clinical trials;
- Ensure that appropriate regulatory pathways are in place to provide rapid but effective regulatory oversight of products to be used in public health emergencies;
- Rarely use domestic clinical trials to generate local data but use extrapolation instead; where justified, the regulator
should define the scientific question to be answered in domestic studies.

WHO
• Support countries in developing consistent approaches to transparency for clinical trial reviews and approvals.
• Strengthen platforms to support capacity-building initiatives for regulatory oversight of clinical trials.
• Facilitate joint reviews of multi-country clinical trial approvals.
• Establish guidelines on regulatory pathways for products to be used in public health emergencies.

Workshop L

Current topics and future developments

Member States
• Promote innovative approaches to enhancing quicker access of medicinal products, without compromising safety;
• Future-proof regulatory approaches and gain insight into newer emerging products through horizon-scanning; interact with stakeholders and collaborate;

• With other national regulatory authorities, garner support for appropriate resources and funding to be better prepared in tackling the safety, quality and efficacy of these emerging products.
• Member States are encouraged to engage in multilateral cooperative networks with other regulators, which will facilitate information-sharing and provide mutual benefit for participants; and
• Member States are encouraged to join or draw benefits from multinational initiatives aimed at sharing best practices and expertise, achieving regulatory convergence of requirements as well as work-sharing, e.g. the International Generic Drug Regulators Pilot (IGDRP), the International Medical Device Regulators Forum (IMDRF) and the International Pharmaceutical Regulators Forum (IPRF).

WHO
• Support NMRAs in decision-making by provision of models for regulatory information-sharing and collaboration, including suitable IT instruments/tools.
• Expand existing WHO collaborative procedures for information-sharing.
WHO Prequalification

Ensuring global availability of quality-assured vaccines

WHO supports Member States in providing safe, effective, high quality vaccines against diseases of public health importance. The WHO prequalification programme ascertains that products meet acceptable standards for use in national immunization programmes. Its activities are coupled with regulatory capacity-building to help develop sustainable mechanisms for vaccines quality assurance in Member States. WHO prequalification also facilitates international harmonization of vaccine production standards.

This article gives some background about this long-standing programme and outlines progress and challenges encountered in recent years.

Background
Immunization is key to protecting children from diseases, including polio, measles, diphtheria, and tetanus. Vaccination is one of the most cost-effective health interventions.

To increase access to vaccines of assured quality and safety in Member States, WHO introduced a vaccine prequalification programme in 1987 as a service to UNICEF and other UN purchasing agencies. The norms and standards used for vaccine prequalification are developed in consultation with a wide range of stakeholders. In the 25 years of its existence the prequalification programme has adjusted its procedures to the changing needs.

As more countries routinely immunize children and develop more ambitious national vaccination programmes, the demand for quality products is growing. From 2000 to 2013 the value of the global vaccine market has quadrupled from USD 5 billion to almost USD 24 billion. The number of prequalified vaccines has also grown. The online list on the WHO website includes more than 120 products of 36 different vaccine types, including those that have been in use for a long time – such as diphtheria/tetanus/pertussis vaccine combinations, yellow fever vaccine and oral polio vaccine – as well as new ones, such as pneumococcal conjugate vaccine, rotavirus and human papillomavirus vaccine. Each year, WHO-prequalified vaccines are used to immunize 65% of the world’s birth cohort.

Regulatory oversight
Vaccines are complex biological products. To ensure that all vaccines used by national immunization programmes meet the required standards of quality, safety and efficacy, WHO works in partnership with national regulatory authorities (NRAs) to provide lot-to-lot oversight. In 1996 WHO launched an initiative to strengthen NRAs. An assessment tool was developed to monitor progress and to provide a benchmark for vaccine prequalification for purchase by United Nations agencies. Over the years the tool was revised several times with input from more than one hundred countries. The current version dates from 2011.
Assessment of NRAs using this tool gained a new significance in 2002, when the decision was adopted that the WHO prequalification programme will accept submissions from vaccine manufacturers only if the NRA of the producing country has been assessed as functional against the indicators defined in the assessment tool. This decision has greatly supported WHO efforts to strengthen capacity for vaccine regulation in developing countries.

For the last five years, WHO’s regulatory capacity-building measures have been targeted strategically to emerging economies which impact global vaccine supply. This strategy has a dual goal: to sustain existing functionality of NRA in countries with already prequalified manufacturers, and to strengthen the NRAs of countries with manufacturers interested in vaccine prequalification.

At the end of 2013, 35 of 43 vaccine-producing countries around the world were assessed as functional according to WHO indicators. Of these, 22 supplied at least one WHO-prequalified vaccine, thus broadening the supplier base for safe and effective vaccines of good quality. For example, maintaining functionality, since early 2011, of the China Food and Drug Administration (CFDA) was the catalyst for WHO prequalification of the first vaccine from China in 2012, a live attenuated Japanese encephalitis vaccine. Prequalified vaccines are produced in seven other low- and middle income countries: Brazil, Bulgaria, Cuba, India, Indonesia, Senegal and Thailand.

**Engagement with manufacturers**

As increasing numbers of vaccines come from countries with NRAs recently declared as functional, there is a need to familiarize manufacturers with the quality standards required by the WHO prequalification programme. In addition to providing detailed online guidance on prequalification requirements and processes, the prequalification team is engaging with manufacturers before submission of applications. This activity has grown significantly in past years. The number of one-on-one meetings with manufacturers increased from 40 in 2008 to 131 in 2012.

The improved guidance has helped to decrease the average time spent by WHO assessors on evaluating dossiers substantially. From 2007 to 2013 the average time from application to prequalification – excluding periods spent waiting for additional data – has almost halved, from 350 to 138 days.

**Streamlined procedures**

A major revision of the vaccines prequalification process was adopted in 2010 and came into force in January 2012 (5). The revised procedure introduced two significant changes.

Firstly, taking into account the increasing need for regulatory collaboration and risk-based approaches, the revised procedure provides the option for fast-tracked assessment. This option is used if WHO has an official agreement for information-sharing with a mature NRA responsible for the product, usually that of the producing country. The fast-track process shortens the average assessment time. In 2013 WHO assessors spent an average of 82 days on dossiers submitted under this process, compared to 138 days for the standard process.

Secondly, the revision also introduced written criteria defining programmatic suitability for prequalification (6). This addresses a previously unmet need to provide manufacturers with clarity on the desired product design features for use...
in immunization programmes receiving vaccines through UN procurement. Manufacturers now routinely consult WHO at an early stage of developing products for prequalification. This interaction has reduced the time taken by WHO assessors to consider products with non-compliant characteristics.

**Post-prequalification activities**

Even if dossier assessment can be fast-tracked for products from countries with mature regulatory authorities, WHO remains responsible for ensuring compliance with UN tender specifications and programme needs, monitoring product quality and safety, and conducting a targeted testing programme. If there are quality concerns, the supply of prequalified vaccines can be suspended, or the product can be delisted from WHO’s prequalification list. A complete record of issues relating to prequalified vaccines is published on the WHO website (7).

WHO’s post-prequalification work consists of both planned and unplanned activities, which have been increasing over the years as more vaccines have become prequalified (Figure 1). Regular maintenance causes a significant workload; for example the 53 product reviews done in 2012 gave rise to assessment of 448 variations (changes) to prequalified vaccines. In addition, unplanned but urgent activities arise whenever complaints or reports adverse events following immunization (AEFI) are received from the field.

**Prequalification of immunization equipment and devices**

WHO prequalifies not only the actual vaccines but also a comprehensive range of cold chain equipment, injection devices and other products needed for safe and effective immunization delivery. The Performance, Quality and Safety (PQS) scheme for the prequalification of equipment and devices for immunization was introduced in 2006 and became functional gradually during a transition.
period from the previous PIS (Product Information Sheet) system.

The PQS approach to equipment and device prequalification encourages the continuous improvement of existing products whilst remaining open to innovation. The scheme is based on three key criteria for products:

- Performance characteristics that meet the relevant specification standards;
- Quality and reliability characteristics that are appropriate for field conditions, and
- Safety characteristics that ensure that no harm is caused to users, patients or the environment over the course of the product’s life cycle.

In recent years the number of accessory products prequalified through the PQS scheme has increased more than fourfold, from 55 in 2008 to 245 at the end of 2013 (8). As more and more countries are now including requirements for PQS prequalification in their tenders, the scheme goes far beyond UN purchasing. It provides procurement agencies around the world with a list of reliable immunization equipment and devices, each proven to meet user needs.

**Regulatory capacity-building**

The prequalification programme uses two strategies to promote the implementation of WHO norms and standards for vaccines in countries.

Firstly, regulators from a wide range of WHO Member States are invited to participate in expert meetings to develop WHO standards. The focus is on the review of scientific evidence for clinical evaluation of vaccines. In this way, participating regulators acquire the specific expertise needed to drive the implementation of the agreed standards actively in their own regulatory environments.

Secondly, WHO organizes implementation workshops for new written WHO standards, using practical examples and case studies. Vaccine lot release, stability evaluation, safety of cell substrates for vaccine production and Good Manufacturing Practice (GMP) are examples of priority topics covered.

**Vaccine safety**

Post-approval surveillance is essential to confirm that vaccines are safe to use in the target populations. To follow up on the safety of vaccines used in Member States WHO created a functional network of countries, including some of the most advanced in terms of vaccine pharmacovigilance.

The participating countries have played a key role in advancing vaccine safety worldwide. They contributed to the Global Vaccine Safety Blueprint objectives (9), leading to the launch of the Global Vaccine Safety Initiative in November 2012 (10). They also proposed implementation models to achieve these objectives and shared their experience with other countries. Regional vaccine safety networks in line with the globally recommended model are being established in three WHO regions: the Eastern Mediterranean Region, the Region of the Americas and the South-East Asia Region.

A key outcome from the network was the definition of a minimum core data set to be collected for AEFI (11). A standard AEFI reporting form was designed and implemented in network countries. In parallel, a simple, vaccine-specific electronic user interface was developed and has meanwhile been pilot-tested successfully in one country.

The network has provided a good understanding of the opportunities and challenges of managing vaccine safety in...
low- and middle-income countries. Each of the network countries has faced major hurdles. Nevertheless, most have made significant progress in detecting and reporting AEFI, and some are now moving beyond minimal capacity to participation in epidemiological risk assessment studies. Valuable lessons have been learned that can be used to improve safety management programmes for other health technologies.

**Conclusion**

WHO has prequalified a wide range of vaccines and related products, and has developed streamlined, risk-based processes to assess products in line with current, stringent regulatory principles. This has enabled faster access to a wide range of needed products for WHO Member States and has promoted international norms and standards for vaccines among manufacturers, regulators and procurers.

A significant challenge facing the WHO vaccine prequalification team is the expanding workload to oversee an increasingly complex range of prequalified products. This expansion has not been matched by a similar increase in funding and resources.

In this context it should be noted that the prequalification service provided by WHO is not intended to be a permanent mechanism to ensure the quality, safety and efficacy of vaccines globally. It is therefore crucial for WHO and Member States to continue their regulatory collaboration and capacity-building initiatives, as urged in May 2014 by the Sixty-seventh World Health Assembly (12).

**References and further reading**

2. WHO. Vaccine market [web page].
3. WHO. WHO prequalified vaccines [web page].
6. WHO. Immunization standards. Assessing the programmatic suitability of vaccines candidates for WHO prequalification [web page].
7. WHO. Issues relating to prequalified vaccines [web page].
8. WHO. PQS Catalogue [web page].
10. WHO. The Global Vaccine Safety Initiative (GVSI) [web page].
11. WHO. Global vaccine safety. Core variables for AEFI [web page].
Bringing quality-assured in vitro diagnostics to WHO Member States

The success of treatment programmes and the rational use of medicines depend critically on diagnostic products. In the absence of fully functioning regulatory mechanisms for in vitro diagnostics (IVDs) in many countries, the WHO prequalification of IVDs programme generates independent technical information that can be used by UN agencies, governments and other organizations when selecting IVDs for use in their health programmes.

Since its creation in 2008, the programme has undergone some changes as WHO strives to identify quality-assured IVDs for use in Member States where they are needed most. This article describes the prequalification of IVDs programme, its processes, and how it fulfils its unique role.

Background
Good quality in vitro diagnostics (IVDs) are crucial for informed treatment decisions. Incorrect diagnoses can have profound implications for the individual patient, potentially delaying life-saving treatment, subjecting people to unnecessary medication that can be harmful, and impacting their lives in significant ways. IVDs also play a central role in public health, enabling governments to prevent transmission of communicable diseases, to safeguard blood supplies against contamination, and to allocate limited resources effectively. Quality-assured IVDs are therefore critically important for health systems in WHO Member States.

IVDs are challenging to regulate. Unlike medicines and vaccines they are often produced in significantly different versions for different target markets. They also have fast innovation rates and frequent changes of manufacturer ownership.

Although regulatory systems for IVDs have been evolving globally in recent years, there are still many countries where they are virtually non-existent or limited to purely administrative procedures. This regulatory vacuum has resulted in low cost, but low quality, IVDs being introduced into some markets.

By prequalifying IVDs for use in treatment programmes, WHO aims to promote and facilitate access to safe, appropriate and affordable IVDs of good quality in an equitable manner. The WHO prequalification status, together with other criteria, is considered by UN agencies, WHO Member State governments and other interested organizations in making procurement decisions. It is important to understand, however, that it is not WHO’s mandate to issue approvals, certificates or licenses for IVDs. This responsibility lies with the national regulatory authority of each country.

A recent review has resulted in a streamlined approach to prequalification of IVDs1, taking into account the lessons learned in the programme’s early years and the evolving environment in which it operates. The changes introduce more efficient, transparent and consistent processes, better technical support to manufacturers, and greater integration with

---

1 For details, refer to: http://www.who.int/diagnostics_laboratory/streamlining/en/
the work of other WHO programmes and partners.

**Prioritization**

Prequalification focuses on IVDs for priority diseases and for use in resource-limited settings. Principles and criteria have been defined to prioritize submissions for review, with the overall aim to make needed technologies of good quality available where regulatory mechanisms are lacking *(Box 1)*. The criteria are periodically reviewed in consultation with other UN agencies, WHO programmes and technical experts.

*Box 1. Prioritizing submissions for review*

<table>
<thead>
<tr>
<th>Prioritization principles:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Need for the IVD in managing a particular disease or disease state;</td>
</tr>
<tr>
<td>• Appropriateness of the product for use in resource-limited settings;</td>
</tr>
<tr>
<td>• Requests from WHO Member States for particular IVDs;</td>
</tr>
<tr>
<td>• Performance characteristics of particular IVDs;</td>
</tr>
<tr>
<td>• Availability of other WHO prequalified products that are of a similar test format and/or test principle.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prioritization criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Products already listed on the WHO procurement scheme and procured by UN organizations in significant volumes;</td>
</tr>
<tr>
<td>• Products which assist in:</td>
</tr>
<tr>
<td>- diagnosis and/or monitoring of infection with HIV-1/HIV-2,</td>
</tr>
<tr>
<td>- diagnosis and/or monitoring of infection with hepatitis C, and</td>
</tr>
<tr>
<td>- diagnosis of infection with malaria parasites;</td>
</tr>
<tr>
<td>• Products in a rapid test format and/or technologies that can be used at or near to point-of-care (POC);</td>
</tr>
<tr>
<td>• Products manufactured by original product manufacturers;</td>
</tr>
<tr>
<td>• Products of categories for which there are few other prequalified products.</td>
</tr>
</tbody>
</table>

**Prequalification assessment**

WHO assesses IVDs through a standardized procedure, which includes three components: product dossier review, manufacturing site inspection and laboratory evaluation *(Figure 1)*. The assessment can be terminated at any time if the manufacturer fails to provide required information or take corrective actions as requested by WHO, or if the product does not meet the acceptance criteria for laboratory evaluation.

**Product dossier review**

The product dossier provides evidence in support of the safety and effectiveness of the product. It includes information on product performance, product design and manufacture. An important component is the manufacturer’s quality management system, a hallmark of any quality-assured product. It provides assurance that manufacturing is done under stringently controlled oversight, so that all lots produced over time can be expected to perform consistently.

The prequalification dossier format is based on a model developed by the Global Harmonization Task Force (GHTF)², a group of representatives from the mature regulatory systems of Australia, Canada, the European Union, Japan and the United States. The expected contents of the dossier are described in a guidance text *(2).*

**Manufacturing site inspection**

WHO inspectors visit the sites where IVDs are manufactured to assess

---

² GHTF generated a series of documents identifying best regulatory practice for medical devices that can be applied globally. GHTF was replaced in 2012 by the International Medical Device Regulators Forum (IMDRF), which continues to promote GHTF goals and maintains the guidance documents produced by GHTF.
compliance with the applicable ISO quality management standard (3) and with other relevant international standards and guidelines, notably those produced by GHTF/IMDRF. The WHO inspections focus on verifying whether the manufacturing processes are suitable to ensure a reliable supply of products to WHO Member States. Importantly, the inspectors will also cross-check the content of the product dossier by reviewing reports and raw data on site and by interviewing the personnel involved.

**Laboratory evaluation**
The purpose of the laboratory evaluation is to assess the performance and operational characteristics of the product. The latter are important in understanding how well-suited a product is for use in the destination country.

The laboratory evaluation is carried out by specified WHO Collaborating Centres or designated laboratories under the instructions of WHO. Products are evaluated against predetermined performance criteria established by WHO.

**Abbreviated prequalification assessment**
If a product has already passed a stringent assessment by a mature regulatory system – i.e. a GHTF founding member – then WHO considers that another full assessment would unnecessarily duplicate efforts on the part of both the manufacturer and the assessing entities. For such products the programme offers an abbreviated pathway to prequalification (Figure 2). A product qualifies for abbreviated assessment if:

1. A stringently assessed regulatory version is submitted for prequalification; or
2. A non-stringently assessed (“rest of world”) regulatory version is submitted for prequalification, but a stringently assessed regulatory version also exists and there are no substantial differences between the two regulatory versions.

Under the abbreviated procedure no formal dossier is required. Instead, manufacturers have to maintain a current technical file of which WHO will review certain elements during inspection. However,
WHO will always perform an inspection – in abbreviated form unless there are recent reports of serious concerns – and a laboratory evaluation. This is done because regulatory approval in a given country does not necessarily provide assurance that the product will have the same quality, safety and performance when it is used in other jurisdictions.

Prequalification outcome
Once a product meets WHO prequalification requirements it is added to the list of WHO-prequalified IVDs, stating the specific product name, product code(s) and regulatory version as manufactured at the specific manufacturing site(s) that have been inspected. The list is published on the WHO website along with a public report for each product summarizing the prequalification assessment findings.

After prequalification the manufacturer has to keep WHO informed of any changes to the product and/or to the quality management system under which it was manufactured at the time of prequalification.

Post-market surveillance
While a comprehensive pre-market assessment goes a long way to ensure that a product is well designed and is manufactured under controlled conditions, it does not guarantee safety and performance at the point of use. The successful use of an IVD also depends on a host of downstream factors, from manufacture and transport of products to their storage, maintenance and use by health workers. Detecting, understanding and addressing any shortcomings is crucial for IVD technologies to have the expected impact in treatment programmes.

The purpose of post-market surveillance is to verify that the IVDs supplied to treatment programmes continue to comply with WHO prequalification requirements. This is done proactively through lot verification testing (verifying whether each lot manufactured meets set criteria) and proficiency testing (verifying that valid test results are obtained at the point of use), as well as reactively through systematic reporting of complaints and adverse events, followed by appropriate action. Manufacturers on their part must fulfill their post-market surveillance responsibilities as a condition for WHO prequalification.

Achievements and challenges
Since 2010, when the prequalification of IVDs programme became fully operational, WHO has prequalified a total of 26 IVD products including HIV and malaria rapid diagnostic tests, HIV virological technologies and CD4 technologies.

The programme has experienced a number of challenges in setting up effective prequalification processes for IVDs, which are produced and used in a complex, fast-moving and relatively unregulated environment. Following the implementation of a streamlined approach, work will continue among all stakeholders to shorten the time to prequalification decisions with the overall aim of contributing to faster market access for needed IVDs of good quality.

Conclusion
The WHO prequalification programme fills a niche by assessing IVDs developed for use in resource-constrained settings, where the capacity for regulation and quality assurance of IVDs is often limited. WHO’s independent assessment provides Member States, their procurers and other implementing partners with access to a

---

list of WHO-prequalified IVDs that meet internationally recognized quality, safety and performance standards, along with detailed technical information for each product in public reports. Given the scarcity of regulatory systems for IVDs in many parts of the world, this information represents a significant global public good.

References

1 WHO Prequalification of In Vitro Diagnostics Programme: Overview of the prequalification of in vitro diagnostics assessment, PQDx_007 v5; 30 May 2014.

2 WHO Prequalification of In Vitro Diagnostics Programme. Instructions for Compilation of a Product Dossier. PQDx_018 v2; 30 June 2014.

Medicines quality

Combating unsafe medical products: outcomes of a survey on testing of suspect medicines

Spurious, falsely-labelled, falsified and/or counterfeite products infiltrating the pharmaceutical supply chains continue to pose a global public health risk. Strategic quality control (QC) testing is a cornerstone of the fight against these products. A survey among QC laboratories in all six WHO regions has provided more insight on how this testing is conducted in Member States.

The international health community is becoming increasingly aware of the problem of poor quality medical products, and is determined to tackle this growing challenge to public health. Regulatory authorities and enforcement agencies are working together to implement effective checks and controls. For example, in 2014 Interpol’s annual “Operation Pangea” was supported by 198 agencies around the world (1).

WHO’s role in combating unsafe medicines is to provide information and create awareness, to develop and promote norms and standards for medicines quality assurance, and to provide technical support to build regulatory capacity in Member States (3). Beyond fulfilling its normative role, WHO also offers practical support for example through its prequalification of QC laboratories programme and its External Quality Assurance Assessment Scheme (EQAAS).

Equally importantly, WHO provides a unique forum bringing together Member State governments in the interest of public health. WHO’s globally supported Surveillance and Rapid Alert System for Substandard/Spurious/Falsely labelled/Falsified/Counterfeit (SSFFC) Medical Products has collected over 200 case reports resulting in five international drug alerts since 2012 (2).

While the Rapid Alert System enables governments to take immediate steps against unsafe medical products, the WHO Member State Mechanism on SSFFCs has also led to more long-term action. In Africa, Health Ministers have endorsed plans for regulatory convergence involving the regional economic communities and the African Union Commission (AUC), with the vision to work towards an Africa Medicines Agency. With regard to SSFFC medical products, a regional working group of regulatory, industry and legal experts has been formed to fight the production and circulation of such goods in the WHO African Region. The group met in Brazzaville in July 2014 to review progress, analyze the extent of the problem and provide recommendations to countries (4).

As part of its standard-setting role WHO is envisaging to provide guidance on the use of laboratory techniques to identify suspect products circulating in countries. A

The survey report was prepared by Dr Marius Brits, North West University, Potchefstroom, South Africa, with inputs from Dr Sabine Kopp, Manager, Medicines Quality Assurance Programme, Technologies, Standards and Norms, WHO, Geneva, Switzerland.
range of spectroscopic, chromatographic and other methods have been suggested to detect SSFFC products. Hand-held devices have been developed for use at ports of entry or in remote areas, such as the FDA's Counterfeit Detection Device CD-3 which can be used to screen tablets, packaging and even documents.

A challenge common to most law enforcement checks is that they need ongoing monitoring and refining to prevent circumvention. In this regard, too, the work of WHO with regulators and laboratory experts in Member States offers added opportunities to exchange experiences in real time.

While rapid detection methods can identify suspect products, they cannot replace confirmatory QC testing of pharmaceutical products against their legal specifications. Little is known about the extent and practices of testing actually conducted in countries on suspect medical products. In 2011-2013 the WHO Collaborating Centre for the Quality Assurance of Medicines designed, conducted and analyzed an online survey on this topic among QC laboratories from 39 countries around the world.

The survey results point to a need for more standardized guidance and collaboration on QC testing of suspected SFFC medicines. The findings and recommendations are summarized in Annex 1. The survey respondents are listed in Annex 2.

References
4 We must prevent the production, marketing, and use of unsafe medical products, says Dr Sambo, WHO Regional Director for Africa. [Press release]. WHO Regional Office for Africa; 23 July 2014.
Annex 1. Summary of survey findings

Survey on the testing of spurious/falsely-labelled/falsified/counterfeit (SFFC) medical products
Conducted by the WHO Collaborating Centre for the Quality Assurance of Medicines,
North-West University, Potchefstroom, South Africa
Working document QAS/13.539, December 2013

Table 1. Awareness, policy and standard operating procedures

<table>
<thead>
<tr>
<th>Do you consider SFFCs to be a problem within your country/region?</th>
<th>Yes: 35 (90%)</th>
<th>No: 4 (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does your country have a national policy with regard to testing of SFFCs?</td>
<td>Yes: 26 (67%)</td>
<td>No: 13 (33%)</td>
</tr>
<tr>
<td>Does your laboratory test SFFCs?</td>
<td>Yes: 28 (72%)</td>
<td>No: 11 (28%)*</td>
</tr>
<tr>
<td>(Laboratories which are testing SFFCs:) Do you have a standard operating procedure (SOP) for the testing of SFFCs?</td>
<td>Yes: 10 (36%)</td>
<td>No: 18 (64%)</td>
</tr>
</tbody>
</table>

* Of the 11 respondents whose laboratories did not test SFFC products, six stated that they had access to appropriate laboratory facilities while five stated that they did not.

Table 2. Number of suspected SFFC products tested at the respondent laboratories each year, and proportion found to be SFFC

<table>
<thead>
<tr>
<th>Country where laboratory is located</th>
<th>Number of suspected SFFC products tested annually</th>
<th>Found to be SFFC (Number, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>3748</td>
<td>298 (10%)</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>Approx. 1000</td>
<td>Approx. 4 (0.4%)</td>
</tr>
<tr>
<td>Vietnam</td>
<td>700</td>
<td>47 substandard, 2 counterfeit (6.7%, 0.3%)</td>
</tr>
<tr>
<td>Ghana</td>
<td>417</td>
<td>26 (6%)</td>
</tr>
<tr>
<td>France</td>
<td>300</td>
<td>75 (25%)</td>
</tr>
<tr>
<td>Australia</td>
<td>200-250</td>
<td>170 (68-85%)</td>
</tr>
<tr>
<td>Belgium</td>
<td>200</td>
<td>≈ 60-70%</td>
</tr>
<tr>
<td>Hungary</td>
<td>Approx. 100</td>
<td>95 (95%)</td>
</tr>
<tr>
<td>Colombia</td>
<td>100</td>
<td>50 (50%)</td>
</tr>
<tr>
<td>Thailand</td>
<td>More than 100</td>
<td>Approx. 20%</td>
</tr>
<tr>
<td>Tanzania</td>
<td>86</td>
<td>3 (3.5%)</td>
</tr>
<tr>
<td>Venezuela</td>
<td>75</td>
<td>25 (33%)</td>
</tr>
<tr>
<td>Uganda</td>
<td>65</td>
<td>65 (100%)</td>
</tr>
<tr>
<td>Singapore</td>
<td>76 (2010), 23 (2011)</td>
<td>10%</td>
</tr>
<tr>
<td>Brazil</td>
<td>43</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>Oman</td>
<td>43</td>
<td>13 (30%)</td>
</tr>
<tr>
<td>Mali</td>
<td>30</td>
<td>19 (63%)</td>
</tr>
</tbody>
</table>

Continued

1 The survey focused on testing to detect spurious, falsely-labelled, falsified and counterfeit products, beyond the routine quality control testing for non-compliance with specifications.
Table 2. Continued

<table>
<thead>
<tr>
<th>Country where laboratory is located</th>
<th>Number of suspected SFFCs tested by the laboratory each year</th>
<th>Found to be SFFC (Number, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>15</td>
<td>10 67%</td>
</tr>
<tr>
<td>Moldova</td>
<td>8</td>
<td>1 13%</td>
</tr>
<tr>
<td>Kenya</td>
<td>5</td>
<td>3 60%</td>
</tr>
<tr>
<td>Panama</td>
<td>4</td>
<td>3 75%</td>
</tr>
<tr>
<td>Armenia</td>
<td>2</td>
<td>2 100%</td>
</tr>
<tr>
<td>Chile</td>
<td>2</td>
<td>2 100%</td>
</tr>
<tr>
<td>China</td>
<td>Case by case</td>
<td>None found in the last two years</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Case by case</td>
<td>Case by case</td>
</tr>
</tbody>
</table>

Table 3. Active pharmaceutical ingredients (APIs) targeted in testing of suspected SFFC products (n=23)

<table>
<thead>
<tr>
<th>Class of API</th>
<th>Number of respondents who tested one or more API in that class</th>
<th>APIs mentioned by respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobials</td>
<td>12</td>
<td><strong>Amoxicillin</strong> (4th), ampicillin, cotrimoxazole, penicillin, erythromycin, chloramphenicol, ciprofloxacin, chloramphenicol, meropenem, cefotaxime, tetracycline, cloxacillin, cefuroxime, imipenem, tetracycline</td>
</tr>
<tr>
<td>Genital system</td>
<td>11</td>
<td><strong>Sexual dysfunction medicines:</strong> <strong>sildenafil</strong> (1st), <strong>tadalafil</strong> (2nd), <strong>vardenafil</strong> (4th), dapoxetine</td>
</tr>
<tr>
<td>Gastro-intestinal system</td>
<td>9</td>
<td><strong>Appetite suppressants:</strong> <strong>sibutramine</strong> (4th), diethylpropione, fenproporex <strong>Reversible lipase inhibitor:</strong> orlistat <strong>Proton pump inhibitors:</strong> pantoprazole, omeprazole</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>9</td>
<td><strong>Artesunate</strong> (4th), <strong>pyrimethamine</strong> (3rd), <strong>artemether</strong> (5th), <strong>quinine</strong> (5th), mefloquine, chloroquine phosphate, sulfadoxine, dihydroartemisinin, piperaquine, lumefantrine, amidiaquine, primaquine</td>
</tr>
<tr>
<td>Analgesics and antiinflammatory</td>
<td>9</td>
<td>Paracetamol, diclofenac sodium, aspirin, mefenamic acid</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>4</td>
<td><strong>Androgen &amp; anabolic steroid:</strong> testosteron <strong>Anti-androgen:</strong> cyproterone</td>
</tr>
<tr>
<td>Antiretrovirals</td>
<td>4</td>
<td>(None specified)</td>
</tr>
<tr>
<td>Anti-TB</td>
<td>4</td>
<td>Rifampicin, isoniazid, pyrazinamide, ethambutol</td>
</tr>
<tr>
<td>Endocrine system</td>
<td>2</td>
<td><strong>Anti-diabetic:</strong> metformin, insulin, glibenclamide</td>
</tr>
<tr>
<td>Growth hormones</td>
<td>1</td>
<td>Somatropin</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>Botulinum toxin, cilastatin, aminophylline, diazepam, mebendazole, phenobarbitone, misoprostol, propofol, folic acid, lidocaine, vecuronium bromide, chlorpheniramine, minoxidil</td>
</tr>
</tbody>
</table>
Table 4. Techniques used for the testing of suspected SFFCs (n=26)

<table>
<thead>
<tr>
<th>Technique</th>
<th>Specific</th>
<th>Number of respondents using specific technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromatography</td>
<td>High-performance liquid chromatography (HPLC)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Thin-layer chromatography (TLC)</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Liquid chromatography–mass spectrometry (LC-MS)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Gas chromatography–mass spectrometry (GC-MS)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Gas chromatography–Flame ionization detection (GC-FID)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Ultra-performance liquid chromatography (UPLC)</td>
<td>3</td>
</tr>
<tr>
<td>Spectrophotometry</td>
<td>UV spectrophotometry</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Fourier transform infrared spectroscopy (FTIR)</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Near Infrared (NIR) spectroscopy</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Raman spectroscopy</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Atomic absorption spectrometry (AAS)</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>General chemical tests</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Titration</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Microscopy</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Microbiological tests</td>
<td>2</td>
</tr>
</tbody>
</table>

Challenges faced by respondents in testing SFFCs

The respondents’ comments on challenges associated with testing of suspected SFFC products are listed below, grouped into four broad areas.

Legal framework

- Laws on prosecution of individuals involved in dealing with SFFCs are weak.
- The laboratory does not have a procedure for handling of SFFCs that will protect its interests in case of litigation.

Equipment and resources

- Advanced equipment is not available for the testing of SFFCs.
- Time and resources are lacking to perform confirmatory tests on suspect samples.
- Staff in the laboratory are not trained to perform analysis on SFFC samples.

Standards and methods

- Manufacturer’s specifications and test methods are not available. (*Authors’ comment: Test specifications and methods of analysis are the intellectual property of the manufacturer and therefore not publicly available. Fortunately pharmacopoeial methods are available for most pharmaceutical products, although the testing of some herbal/traditional medicines remains a challenge.*)
- Reference standards for new compounds and their derivatives are not available. (*Authors’ comment: The knowledge of compound derivatization and the identification of all possible derivatives with a specific method remain challenging. The high costs of primary reference standards are another reason why some laboratories resort instead to the use of commercial products to identify known adulterants.*)
- No authentic samples (reference samples) are available of the product being tested.
Knowledge and guidance

- Too few samples are collected at the time of seizing suspected SFFCs, limiting the extent of testing that the laboratory can do.
- The laboratory does not have knowledge of sophisticated analytical methods which could be used to test of SFFC samples.
- Guidance is lacking on how to adapt analytical methods to detect all potential analogues/derivatives of the APIs found in the SFFCs.
- It is difficult to identify unknown adulterants in SFFCs. (Authors' comment: This challenge could also be attributed to a lack of adequate equipment.)
- The laboratory does not have methods or guidance for testing of potentially adulterated herbal products.

Of the 38 respondents who answered all the survey questions, 37 affirmed that their laboratory would benefit from a WHO model standard operating procedure for testing of suspected SFFC products, as well as from training on how to do this testing.

Recommendations

The authors of the survey report recommend to:

Establish a multidisciplinary and collaborative task team that will develop technical guidance, using the following proposed stepwise approach:

1. Consider activities and behaviours that may result in SFFCs, as identified by the WHO Member State Mechanism on SSFFC medical products in line with its Objective 4, stated in Resolution WHA65.19 of the World Health Assembly.
2. Identify properties of SFFCs which are expected to result from the activities and behaviours identified in (1) above.
3. Draft a general procedure for the management and testing of SFFCs by QC laboratories based on the properties identified in (2) above.
4. Draft training manuals and present training sessions to QC laboratories, based on the information outlined in (1) - (3) above.

Create an access-controlled, web-based portal for collaboration and exchange of information.

The portal would offer access to technical guidance as described above, and enable participating laboratories to contribute posts on their own experience in the testing of SFFCs such as examples of SFFCs identified, new techniques developed, and challenges encountered. The portal would be moderated by a technical task team. Over time it will enable participants to build an updated knowledge base on testing of SFFCs.

Annex 2. Survey respondents

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Country</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>Algeria</td>
<td>Laboratoire National de Contrôle Produits Pharmaceutiques</td>
</tr>
<tr>
<td></td>
<td>Burkina Faso</td>
<td>Laboratoire National de Santé Publique (LNSP)</td>
</tr>
<tr>
<td></td>
<td>Cameroon</td>
<td>Laboratoire National de Contrôle de Qualité des Médicaments et d’Expertise (LANACOME)</td>
</tr>
<tr>
<td></td>
<td>Côte d’Ivoire</td>
<td>Laboratoire National de la Santé Publique</td>
</tr>
<tr>
<td></td>
<td>Ethiopia</td>
<td>Product Quality Assessment Directorate</td>
</tr>
<tr>
<td></td>
<td>Ghana</td>
<td>Food and Drugs Board Laboratory</td>
</tr>
<tr>
<td></td>
<td>Kenya</td>
<td>Mission for Essential Drugs and Supplies</td>
</tr>
<tr>
<td></td>
<td>Mali</td>
<td>Laboratoire National de la Santé</td>
</tr>
<tr>
<td></td>
<td>Niger</td>
<td>Laboratoire National de Santé Publique et d’expertise (LANSPEX)</td>
</tr>
<tr>
<td></td>
<td>Senegal</td>
<td>Laboratoire National de Contrôle des Médicaments</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>Research Institute for Industrial Pharmacy Inc (CENQAM)</td>
</tr>
<tr>
<td></td>
<td>Tanzania</td>
<td>Tanzania Food and Drugs Authority (TFDA) Quality Control Laboratory</td>
</tr>
<tr>
<td></td>
<td>Uganda</td>
<td>National Drug Quality Control Laboratory</td>
</tr>
<tr>
<td>Americas</td>
<td>Brazil</td>
<td>Instituto Nacional de Controle de Qualidade em Saúde</td>
</tr>
<tr>
<td></td>
<td>Chile</td>
<td>Laboratorio Nacional de Control</td>
</tr>
<tr>
<td></td>
<td>Colombia</td>
<td>Laboratorios de la Subdirección de Medicamentos y Productos</td>
</tr>
<tr>
<td></td>
<td>Costa Rica</td>
<td>Layafa</td>
</tr>
<tr>
<td></td>
<td>Cuba</td>
<td>Center for Research and Development of Pharmaceuticals</td>
</tr>
<tr>
<td></td>
<td>Jamaica</td>
<td>Caribbean Regional Drug Testing Laboratory</td>
</tr>
<tr>
<td></td>
<td>Panama</td>
<td>Instituto Especializado de Analisis</td>
</tr>
<tr>
<td></td>
<td>Peru</td>
<td>Centro Nacional de Control de Calidad / Instituto Nacional de Salud</td>
</tr>
<tr>
<td></td>
<td>Uruguay</td>
<td>Comisión para el Control de Calidad de Medicamentos (CCCM)</td>
</tr>
<tr>
<td></td>
<td>Venezuela</td>
<td>Instituto Nacional de Higiene “Rafael Rangel”</td>
</tr>
<tr>
<td>South East Asia</td>
<td>India</td>
<td>Central Drugs Laboratory, Kolkata</td>
</tr>
<tr>
<td></td>
<td>Indonesia</td>
<td>Provincial Food and Drug Quality Control, Yogyakarta</td>
</tr>
<tr>
<td></td>
<td>Thailand</td>
<td>Bureau of Drug and Narcotic</td>
</tr>
<tr>
<td>Europe</td>
<td>Armenia</td>
<td>Scientific Centre of Drug and Medical Technology Expertise</td>
</tr>
<tr>
<td></td>
<td>Belgium</td>
<td>Section of Medicines, Scientific Institute for Public Health</td>
</tr>
<tr>
<td></td>
<td>France</td>
<td>Centrale Humanitaire Médico-Pharmaceutique (CHMP)</td>
</tr>
<tr>
<td></td>
<td>Hungary</td>
<td>National Institute of Pharmacy</td>
</tr>
<tr>
<td></td>
<td>Republic of Moldova</td>
<td>Laboratory for Quality Control of Medicines, Medicines Agency</td>
</tr>
<tr>
<td></td>
<td>Ukraine</td>
<td>Laboratory of Pharmaceutical Analysis of the State Expert Center</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>Oman</td>
<td>Central Quality Control Laboratory</td>
</tr>
<tr>
<td></td>
<td>Saudi Arabia</td>
<td>National Drug and Cosmetic Control Laboratories, Saudi Food and Drug Authority, Drug Sector</td>
</tr>
<tr>
<td></td>
<td>Sudan</td>
<td>National Drug Quality Control Laboratory of Sudan</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>Australia</td>
<td>TGA Office of Laboratories and Scientific Services (OLSS)</td>
</tr>
<tr>
<td></td>
<td>China</td>
<td>National Institutes for Food and Drug Control</td>
</tr>
<tr>
<td></td>
<td>Singapore</td>
<td>Pharmaceutical Laboratory, Applied Sciences Group</td>
</tr>
<tr>
<td></td>
<td>Vietnam</td>
<td>National Institute of Drug Quality Control</td>
</tr>
</tbody>
</table>
Safety news

Unchanged recommendations

Olmesartan in diabetic patients: no increased cardiovascular risk
United States of America – The U.S. Food and Drug Administration (FDA) has found no clear evidence of increased cardiovascular risks associated with the use of the blood pressure medication olmesartan in diabetic patients. FDA recommendations for the use of olmesartan will remain the same, but information about some of the studies will be included in the product labels.

The safety review was prompted by an unexpected finding of increased risk of cardiovascular death with olmesartan compared to placebo in a clinical trial in patients with type 2 diabetes.
► FDA Safety announcement, 24 June 2014.

Levonorgestrel and ulipristal emergency contraceptives: suitable for all bodyweights
European Union – The European Medicines Agency (EMA) advises that emergency contraceptives containing levonorgestrel or ulipristal acetate can continue to be used in women of all weights.

An EU-wide review had been triggered by a change to product information for a levonorgestrel-containing contraceptive in an EU country, stating that the product was less effective in women above 75 kg and not effective in women above 80 kg. The review did not confirm that high bodyweight reduces the contraceptive effect.

Restricted use

Bromocriptine: post-partum suppression of lactation only for compelling reasons
European Union – The EMA has advised against the routine use of bromocriptine-containing medicines to stop lactation or to relieve pain or swelling of the breasts after childbirth.

Due to a risk of rare but potentially serious cardiovascular, neurological and psychiatric side effects, bromocriptine-containing medicines should only be used (in strengths up to 2.5 mg) to stop lactation when there are compelling medical reasons, such as avoiding further distress after loss of the baby during or just after childbirth, or in mothers with HIV infection, who should not breastfeed.

Bromocriptine must not be used in women with disorders that increase blood pressure, a history of coronary artery disease or other severe cardiovascular conditions, or a history of severe psychiatric disorders.

Ferumoxytol: hypersensitivity reactions
European Union – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has concluded that the benefits of ferumoxytol (Rienso®), used to treat anaemia in patients with
long-term kidney disease, continue to outweigh the risks. Considering recent reports of serious hypersensitivity reactions, the Committee recommended that ferumoxytol should be given by infusion over at least 15 minutes (instead of by injection), and that it should be contraindicated in patients with any known history of drug allergy.

► EMA. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 7-10 July 2014.

Canada – Health Canada has endorsed new safety information on ferumoxytol (Feraheme®), and the product information has been revised to reflect new usage restrictions. Ferumoxytol is now contraindicated in patients with any allergy to other parenteral iron products or with two or more drug allergies. The product should be administered with special precautions to mitigate the risk of anaphylaxis and other hypersensitivity reactions.


Intravenous ondansetron: dosage restrictions in patients over 65

Canada – The manufacturer, in consultation with Health Canada, has recommended dosing restrictions for intravenous (IV) ondansetron (Zofran®) in patients above 65 years of age. The same action had been taken earlier by the FDA and the EMA to mitigate the risk of QT prolongation, which can lead to potentially life-threatening heart arrhythmia.

In patients aged 75 years or more the initial IV dose of ondansetron must not exceed 8 mg, while in patients aged 65 to under 75 years it must not exceed 16 mg. Subsequent IV doses must not exceed 8 mg and may be given 4 and 8 hours after the initial dose. All IV doses must be diluted in 50–100 mL of saline or other compatible fluid and infused over no less than 15 minutes. The product information has been updated. – There are no changes to the recommended oral dosing.

Health Canada also reminds health professionals that in patients over 65 years of age ondansetron should be used only to prevent chemotherapy-associated (but not post-operative) nausea and vomiting.

► Health Canada Advisory, 12 June 2014.

Influenza vaccine (Fluvax®): not to be used in children under five

Australia – The company bioCSL has published its research into fever and fever-related convulsions that occurred with its influenza vaccine (Fluvax®) in 2010 in children under five years of age. These adverse events were most likely caused by a stronger immune response due to the introduction of new viral strains in that season’s vaccine, as well as certain extra viral components generated under the standard production method.

The Therapeutic Goods Administration (TGA) has not approved the product for use in children under the age of five. In children aged five to under nine years, health professionals should carefully consider the benefits and risks of vaccinating each individual child with the 2014 bioCSL Fluvax vaccine. The product information has been updated. Additional warnings are also provided on the packaging and for display on vaccine refrigerators.

► TGA News, 12 June 2014.
Etonogestrel / ethinyl estradiol vaginal ring: contraindications

Canada – The manufacturer, in consultation with Health Canada, has spelled out new contraindications in the product information of etonogestrel / ethinyl estradiol slow release vaginal ring (Nuvaring®). The product should not be used by women aged over 35 who smoke, or by those who have severe or multiple risk factors for thrombosis, including: valvular heart disease with complications, hypertension, severe dyslipoproteinaemia, abnormality in proteins that regulate coagulation, diabetes mellitus with vascular involvement, or major surgery with prolonged immobilization. Neither should the product be used by women who have experienced migraines with focal neurological symptoms, or those who suffer from pancreatitis associated with severe hypertriglyceridaemia.

In November 2013 the EMA had advised against using combined hormonal contraceptives in women with one severe risk factor, or multiple risk factors, for blood clots.


Safety warnings

Lidocaine oral viscous solution: not to be used in teething pain

United States of America – The FDA has warned that oral viscous lidocaine 2 percent solution should not be used to treat teething pain, an indication for which the medicine is not approved in the United States.

Overdosing or accidental ingestion of lidocaine can cause seizures, severe brain injury, heart problems and death. The FDA is requiring a new Boxed Warning and revisions to the Warnings and Dosage and Administration sections of the product label to highlight this information.

More generally, the FDA advises parents and caregivers not to use over-the-counter topical medications for teething pain. A 2011 communication had warned against benzocaine gels as they can cause methaemoglobinemia, a rare but life-threatening adverse effect decreasing the amount of oxygen carried through the blood. Instead, teething pain can be relieved by using a chilled (not frozen) teething ring, and by gently rubbing or massaging the child’s gums with a finger.

► FDA Safety announcement, 26 June 2014.

Terconazole cream: rare but serious allergic reactions

Canada – The manufacturer, in consultation with Health Canada, has informed the public that very rare but serious or even life-threatening adverse reactions of anaphylaxis or toxic epidermal necrolysis have been reported during treatment with terconazole vaginal cream (Terazol®). The product is approved for the local treatment of vulvovaginal candidiasis (moniliasis). The Canadian product monograph has been updated to include this new safety information.

Patients should be counseled about these risks, and should be instructed to discontinue use of the medicine if signs of serious allergic reactions occur.

► Health Canada Advisory, 9 June 2014.

Docetaxel: alcohol intoxication

United States of America – The FDA warns that the intravenous chemotherapy medicine docetaxel contains alcohol, which may cause patients to experience intoxication or feel drunk during and after treatment. Some medications, such as
pain relievers and sleep aids, may worsen these effects.

Patients should avoid driving, operating machinery or performing other activities that require alertness for one to two hours after infusion of docetaxel. Health care professionals should consider the alcohol content of the specific docetaxel-containing product when prescribing or administering the medicine to patients, and should monitor and counsel patients appropriately. The FDA is revising the labels of all docetaxel-containing products to warn about this risk.

► FDA Safety announcement, 20 June 2014.

Topical acne products: rare but serious hypersensitivity reactions

United States of America – The FDA is warning that certain over-the-counter topical acne products containing benzoyl peroxide or salicylic acid can cause rare but serious and potentially life-threatening allergic reactions. These products are available as gels, lotions, face washes, solutions, cleansing pads, toners, face scrubs and other products under various brand names.

Consumers should stop using the product and seek emergency medical attention immediately if they experience throat tightness, difficulty breathing, feeling faint, or swelling of the eyes, face, lips or tongue. Consumers should also stop using the product if they develop hives or itching. The reactions may occur within minutes to a day or longer after product use. They differ from local skin irritations at the product application site, such as redness, burning, dryness, itching, peeling or slight swelling, that are already included in the product labels.

The FDA is encouraging manufacturers to include directions on the product labels, instructing consumers to apply a small amount to a small affected skin area for three days before using a topical acne product for the first time. The product should only be used if no discomfort occurs, and if the consumer has not previously experienced adverse reactions to it.


Testosterone: heart and blood vessel problems

Canada – Health Canada has completed a safety review on testosterone replacement products, and has found a growing body of evidence from various sources for serious and possible life-threatening heart and blood vessel problems with the use of these products.

The agency reminds health professionals that testosterone products should only be used to treat low testosterone levels in men as confirmed by laboratory testing. Patients should be assessed for any cardiovascular risk factors or past events before therapy is initiated, and should be closely monitored thereafter.

Health Canada will continue to work with FDA and EMA to address this safety concern.


Paracetamol: rare but severe skin reactions

New Zealand – Medsafe has warned that paracetamol is associated with a risk of rare but serious skin reactions, as recently communicated by the FDA. Patients should consult their doctor at the first appearance of a skin rash, skin peeling, mouth ulcers, or any sign of hypersensitivity. If serious skin reactions...
occur, paracetamol should be stopped immediately.

The New Zealand Centre for Adverse Reactions Monitoring (CARM) has received four reports of serious skin reactions causally associated with paracetamol. These included two reports of erythema multiforme, one of toxic epidermal necrolysis and one of Stevens Johnson Syndrome.

Non-steroidal anti-inflammatory drugs (NSAIDs) can also cause skin reactions. There does not appear to be cross-sensitivity between paracetamol and NSAIDs.

U.S. FDA Safety Announcement, 1 August 2013.
Medsafe. NSAIDs can SCAR (Severe Cutaneous Adverse Reaction). Prescriber Update 33(2): 11-12.

Ofatumumab: fatal infusion reaction
Canada / European Union – The manufacturer, in agreement with regulatory authorities, has informed health professionals about a fatal infusion reaction during administration of the first dose of ofatumumab (Arzerra®) to a patient with chronic lymphocytic leukaemia with no known history of cardiac disease.

Even with premedication as prescribed in the product information, severe infusion reactions can still occur. Health care professionals should inform their patients of this risk. If a severe infusion reaction is suspected, the infusion should be stopped immediately and the symptoms should be treated. Ofatumumab should be given under the supervision of an experienced doctor and in an environment with adequate facilities to monitor and treat infusion reactions. The Canadian product information is being updated to include this information.

EU regulatory authorities have reminded health professionals that infusion reactions have also occurred with other anti-CD20 monoclonal antibodies such as rituximab and obinutuzumab. Recommendations to reduce this risk are found in the summary of product characteristics for each product.

► Health Canada advisory, 6 August 2014.
MHRA Drug safety advice, 7 August 2014.

Fentanyl patches: accidental exposure can be life-threatening
European Union – The marketing authorization holders, in agreement with regulatory authorities, have reminded health professionals that accidental exposure to fentanyl patches can cause life-threatening harm, particularly in children. Patients and caregivers should be advised to:
• choose the patch application site carefully (see patient information leaflet);
• check the adhesion of the patch once applied, especially the edges;
• fold the used patch as soon as it is removed so that its adhesive side sticks firmly to itself, then dispose of it safely;
• if a patch is transferred to another person, remove it immediately and seek medical advice; and
• if a patch is swallowed, seek medical help immediately.

The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has performed an EU-wide review. In addition to the above safe handling measures the PRAC has recommended that the visibility of fentanyl patches should be improved.

► MHRA Drug safety message, 18 June 2014.
Sugammadex: ventricular fibrillation, ventricular tachycardia and coronary arteriospasm

Japan – The Pharmaceuticals and Medical Devices Agency of Japan has warned that cases of coronary arteriospasm, ventricular fibrillation and ventricular tachycardia have been reported in patients treated with sugammadex in Japan. The medicine is used to reverse the effect of muscle relaxants vecuronium and rocuronium, which are administered to support mechanical ventilation or intubation during surgery.

The product information already included a warning about the risk of marked bradycardia and/or cardiac arrest after injection of sugammadex. A warning has been added about the above-mentioned adverse effects, which can occur within minutes after administration. Patients should be carefully monitored and appropriate measures taken in case of any abnormalities.

► PMDA Revision of precautions: Sugammadex sodium. 6 August 2014.

Interferon beta products: thrombotic microangiopathy and nephrotic syndrome

European Union – EMA has endorsed new safety information in response to cases of thrombotic microangiopathy (TMA) including fatal cases, and nephrotic syndrome reported with interferon beta used to treat multiple sclerosis. Both conditions may develop weeks or even years after starting treatment.

Health professionals should suspect TMA if they observe thrombocytopenia, new onset hypertension, fever, central nervous system symptoms and impaired renal function, and should confirm the diagnosis based on blood platelet and serum lactate dehydrogenase levels, renal function tests, and red blood cell fragments on a blood film. TMA must be treated promptly (considering plasma exchange), and immediate discontinuation of interferon beta is recommended.

Health professionals should also look out for signs of nephrotic syndrome, especially in patients at high risk of renal disease, treat promptly if it occurs, and consider stopping interferon beta.

► EMA safety information, 24 August 2014.

Topiramate: Visual field defects

New Zealand – The manufacturer, in agreement with Medsafe, has informed health professionals that visual field defects have been reported in patients receiving topiramate tablets, independently of elevated intraocular pressure. In clinical trials, most of these events were reversible after topiramate discontinuation. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the medicine.

► Medsafe Safety information, 5 August 2014.

Suspended

Methadone with high molecular weight povidone: to be reformulated

European Union – The EMA has endorsed the recommendation to suspend the marketing authorization for oral methadone solutions containing high molecular weight povidone until they have been reformulated to prevent abuse. Methadone tablets that contain low molecular weight povidone will remain on
the market with changes to the product information to reinforce the message that tablets are for oral administration only.

Methadone is used in rehabilitation programmes to prevent or reduce withdrawal symptoms in people dependent on opioids. Some patients misuse oral methadone solutions by injecting them into a vein. The povidone is then not easily excreted from the body and accumulates inside the cells of vital organs, which may cause serious harm.


Overview of safety reviews started

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Uses</th>
<th>Concerns</th>
<th>Reviewing authority reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic ibuprofen-containing medicines</td>
<td>Widely used for pain, inflammation and fever; well-known safety profile, particularly at usual doses</td>
<td>Cardiovascular risk with high dose regimen (2 400 mg per day) taken over long periods; possible interactions with low-dose aspirin (taken to reduce the risk of heart attacks and strokes)</td>
<td>► EMA Press release, 13 June 2014.</td>
</tr>
<tr>
<td>Ivabradine (Coralan®)</td>
<td>Treatment of heart failure and stable angina</td>
<td>Increased combined risk of death and non-fatal heart attack compared to placebo, as identified in preliminary results of the SIGNIFY study</td>
<td>► TGA Monitoring communication, 23 June 2014 (and see EMA Press release, 8 May 2014).</td>
</tr>
</tbody>
</table>

Medicines quality issues

Update on anti-cancer medicines stolen in Italy

European Union – The investigation of the supply of stolen vials of pemetrexed, trastuzumab and infliximab has identified two additional products – bevacizumab and rituximab – that have been distributed illegally from Italy. A document is available on the EMA website that lists the batches concerned by the investigation. EMA had announced the theft on 16 and 17 April 2014.

► EMA News, 3 June 2014.

EMA reinstates GMP certificate for Ranbaxy’s Toansa site

European regulatory authorities have finalized their assessment of reported non-compliance with Good Manufacturing Practice (GMP) at Ranbaxy Laboratories’ manufacturing site in Toansa, India, and have concluded that the deficiencies do not pose a risk to public health. The EU authorities will therefore reinstate the GMP certificate which was suspended in January 2014.

The assessment followed an FDA inspection which had revealed areas of non-compliance with GMP at the site. An international team of inspectors conducted an unannounced inspection and found that the manufacturer has taken appropriate corrective and preventive measures. In
addition, samples of the medicines on the EU market were tested and found to meet the approved quality specifications.

European regulatory authorities will continue watching the Toansa site closely in collaboration with their counterparts in India and around the globe.

► EMA Press release, 5 June 2014.

Compounded products from two U.S. facilities may not be sterile

United States of America – The FDA has alerted health care professionals not to use medicines marketed as sterile produced by two compounders, namely Downing Labs LLC, also known as NuVision Pharmacy, and Unique Pharmaceuticals Ltd.

FDA inspections at the facilities have revealed insanitary conditions, resulting in a lack of sterility of the products and putting patients at risk of infection.

Compounding operations have been repeatedly linked to medicines quality problems. The FDA has outlined strengthened expectations for this type of manufacturing (see page 333).

► FDA Drug alert, 18 July 2014.

Micro Labs Hosur manufacturing site gets WHO notice of concern

Geneva – The WHO Prequalification team has issued a Notice of Concern about Micro Labs Ltd.’s manufacturing site in Hosur, Tamil Nadu, India, following a WHO inspection in February 2014.

If the deficiencies observed during the inspection are not addressed within the recommended time frame, WHO may consider suspending the prequalification of products manufactured at the site, and/or recommend suspending their procurement by UN and other international agencies.

► WHO Prequalification Update, 6 June 2014.

Ipca halts API shipments to the U.S.

India – Ipca Laboratories Ltd has voluntarily suspended shipments of active pharmaceutical ingredients (APIs) to the United States from its manufacturing site at Ratlam after an FDA inspection found non-compliances with Good Manufacturing Practice (GMP). Health Canada then asked Ipca Laboratories to voluntarily stop shipment of products to Canada, and asked Canadian companies to temporarily quarantine any products containing APIs from Ipca. The company is working to address the deficiencies. Neither the FDA nor Health Canada have requested a recall of products already on the market.

WHO has prequalified a number of APIs and finished products which may incorporate APIs manufactured at the Ratlam site. The WHO prequalification programme advises that no issues have been reported that directly impact product quality. It has issued an information note with details of the products concerned, action taken by WHO, and advice to procurement agencies on how to verify that the manufacturers responsible for the products have taken adequate measures to ensure that all batches meet agreed quality standards.

Health Canada Advisory, 17 September 2014.
Regulatory news

Data-sharing

EMA Board agrees on clinical trial data-sharing policy
European Union – The EMA Management Board has reached agreement on its policy on publication of clinical trial data, together with more user-friendly amendments (1). The policy will allow EMA to proactively publish clinical trial data for downloading, saving and printing for academic and non-commercial research purposes. It is expected to become effective from 1 October 2014. Importantly, it will not prejudice citizens' rights under existing access to documents legislation and the new clinical trials regulation.

In a separate process, EMA is now making summaries of the results of clinical trials publicly available (2). From 21 July 2014 applicants are required to upload summary results to the newly upgraded European Clinical Trials Database (EudraCT), from where the result-related information is fed into the EU Clinical Trials Register. Information on clinical trial protocols in third countries is also uploaded to EudraCT if the trials are included in a Paediatric Investigation Plan (PIP), submitted by applicants early in product development to show how a medicine will be studied in children. In July 2014, EMA started publishing PIPs on its website (3).

► (1) EMA News, 12 June 2014
(2) EMA News, 19 June 2014.

Canada advances transparency legislation
Canada – The Government of Canada has welcomed transparency amendments in a proposed patient safety law named Vanessa’s Law (Bill C-17). The amendments provide for disclosure of both positive and negative drug authorization decisions, and clinical trial information and possible disclosure of confidential business information on products that may pose a serious risk to Canadians.

Bill C-17 has been passed in the House of Commons and moves to the Senate for consideration. The amendments would strengthen Health Canada’s Regulatory Transparency and Openness Framework announced in April 2014.


FDA launches public data access platform
United States of America – The FDA has launched openFDA, a new initiative to make it easier for the public to access large public health datasets collected by the agency. The data will be provided in a structured, computer-readable format enabling searches, queries and downloads of public information directly from FDA datasets.

The initial pilot version of openFDA provides access to anonymized reports on drug adverse events and medication errors submitted to the FDA from 2004 to 2013. The pilot will later be expanded to include the FDA’s databases on product
recalls and product labeling. Additional public datasets may follow.
► FDA News release, 2 June 2014. openFDA can be accessed at: https://open.fda.gov/

Generics

Generic registration information-sharing pilot launched
European Union – The European Union’s decentralized procedure – which serves to authorize certain medicines in parallel in more than one EU Member State – is being used as a model to accelerate the assessment of applications for generic medicines as part of the International Generic Drug Regulators Pilot (IGDRP). If an applicant wishes to market the same generic product in the EU through the decentralized procedure and in other jurisdictions that form part of the pilot, the EU will share its assessment reports in real time with collaborating authorities outside the EU. This should enable medicines to be authorized in different territories in a coordinated way at approximately the same time. (1)

The first phase of the pilot will involve the EU, Australia (2), Canada, Chinese Taipei and Switzerland (3). IGDRP members that may decide to take part at a later stage include Brazil, China, Japan, Korea, Mexico, New Zealand, Russia, Singapore and South Africa. The European Directorate for the Quality of Medicines & Healthcare (EDQM) and WHO participate as observers.
► (1) EMA News, 7 August 2014.
(2) TGA news, 12 August 2014.
(3) Swissmedic announcement, 31 July 2014.
More information on the IGDRP: The International Generic Drug Regulators Pilot. WHO Drug Information. 28(1); 2014:3-10.

Regulatory oversight

Canada implements labelling changes for opioids, adopts plain language labelling regulations
Canada – The Government of Canada is implementing new labelling provisions for all classes of controlled and extended release non-generic opioid pain medicines, with standardized wording that more clearly outlines safety concerns for children from accidental exposure and for newborns exposed during pregnancy. The wording also provides clearer prescriber guidance on the use of opioids, which are indicated for daily, long-term management of opioid-responsive severe pain for which alternative treatment is not adequate. Similar label changes will soon be implemented for generic opioids. (1)

Under its Plain Language Labelling Initiative, the government has also finalized new regulations for all medicines, to be phased in gradually. Key safeguards include clear wording on labels and packaging; a standardized format for non-prescription medicines labels; mandatory contact information on labels; mandatory provision by manufacturers of label and packaging mock-ups for Health Canada review; and “Look Alike - Sound Alike” provisions for manufacturers to provide evidence that their product names will not be confused with those of other authorized products. (2)
► (1) Health Canada Information Update. 18 August 2014.

FDA outlines expectations for medicines compounding
United States of America – The FDA has issued several policy documents to support the implementation of new
compounding provisions enacted into law in November 2013.

The new law distinguishes between two types of compounding operations: Section 503A applies to pharmacies that do small compounding operations mainly in response to prescriptions, while Section 503B applies to outsourcing facilities that compound large quantities of sterile products without prescription to cater for a lack or shortage of FDA-approved finished products.

Four policy documents have been published for comment: A draft interim guidance text on GMP expectations under Section 503B with a focus on sterility and general patient safety, a rule that would modify the list of drugs which may not be compounded at all, and two revised requests for nomination of active pharmaceutical ingredients that may be used to compound products under each of the two sections.

► FDA News release, 1 July 2014.

FDA proposes new guidance for certain types of diagnostics

United States of America – The FDA has taken two steps to strengthen its oversight over certain diagnostic tests.

Firstly, the Agency has issued a final guidance on the development, review and approval or clearance of companion diagnostics. These are diagnostic tests designed to guide decisions on treatment with specific medicines for individual patients, for example in certain types of cancer. The guidance aims to foster early coordinated development of medicines and their companion tests.

Secondly, the FDA has given the legally required notice of its intention to publish a proposed risk-based oversight framework for tests which are designed, manufactured and used within a single laboratory. The guidance proposes to enforce a pre-market review for certain laboratory-developed tests (LDTs), starting with those that have the same intended use as FDA-approved or cleared companion diagnostics marketed by conventional manufacturers. However, the framework would not be extended to low-risk LDTs, LDTs for rare diseases and, under certain circumstances, LDTs for which there is no FDA-approved or FDA-cleared test.


Orphan medicines

Canada pilot project seeks patient perspectives on orphan medicines

Canada – As part of its Orphan Drug Framework to spur innovation and research, Health Canada is embarking on a pilot project that will simulate how input from patients will be gathered and incorporated into the review process for orphan medicines.

Two manufacturers have agreed to participate with their registration submissions for new medicines intended to treat chronic lymphocytic leukaemia and urea cycle disorders respectively. Patients will be asked to comment on how these disease affect their day-to-day lives, what treatments are currently available to them, what therapeutic benefits are most important to them, and what risks they are willing to take with new treatments. Once implemented, this process will ensure that patient perspectives are considered in future orphan medicine authorizations.

Submitted for approval

Malaria vaccine
Product name: RTS,S
Submitted to: EMA (Article 58 procedure for intended use outside the EU)
Intended use: Prevention of infection with *Plasmodium falciparum*. In the phase III efficacy trial, RTS,S was administered in three doses, one month apart.
Benefits: In the 18 months efficacy trial the vaccine prevented many cases of clinical and severe malaria. The highest impact was found in areas with the greatest malaria incidence. The vaccine efficacy was higher in children than in infants. To date there is no licensed vaccine available for the prevention of malaria. An effective vaccine for use alongside other measures such as bednets and anti-malarial medicines would represent an advance in malaria control.

Approved

Inhaled insulin (human) for diabetes
Product name: Afrezza® Inhalation Powder
Class: Rapid-acting inhaled insulin;
ATC code: A10AF01
Approval: FDA
Use: Improvement of glycaemic control in adults with diabetes mellitus. The product is administered at the beginning of each meal. In patients with type 1 diabetes it must be used in combination with long-acting insulin.
Safety information: Due to a serious risk of acute bronchospasm in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease, the product should not be used in these patients. It is not recommended for the treatment of diabetic ketoacidosis, or in patients who smoked. The product was approved with a risk evaluation and mitigation strategy and with requirements for post-marketing studies.

Eliglustat for Gaucher disease
Product name: Cerdelga®
Class: glucosylceramide synthase inhibitor;
ATC code: A16AX10
Approval: FDA (orphan drug designation)
Use: Long-term treatment of adult patients with Type 1 Gaucher disease, a rare genetic disorder causing fatty materials to collect in the spleen.
Benefits: Additional treatment option; equally safe and effective as enzyme replacement therapy in stabilizing haemoglobin level, platelet count and spleen and liver volume.
＞ FDA News release, 19 August 2014.

Recombinant antihaemophilic factor for haemophilia A
Product name: Eloctate®
Class: Recombinant antihaemophilic factor, Fc fusion protein (first-in-class)
Approval: FDA (orphan designation)
Use: To control and prevent bleeding episodes, manage bleeding during surgical procedures, and to prevent or reduce the frequency of bleeding episodes in adults and children with haemophilia A.
Benefits: This recombinant product lasts longer than other Factor VIII products in the patient’s blood, requiring less frequent injections for prophylaxis.
＞ FDA News release, 6 June 2014.

Daclatasvir for chronic hepatitis C
Product name: Daklinza®
Class: NS5A inhibitor (first-in-class);
ATC code: J05AX14
Approval: EMA (accelerated assessment)
Use: Treatment of chronic hepatitis C virus infection in adults, in combination with other medicines.
Benefits: Interferon-based combination therapies for hepatitis C have potentially serious side effects that can be difficult to manage. Daclatasvir has been shown to be effective in combination with sofosbuvir...
with or without ribavirin, providing an interferon-free treatment option for hepatitis C.

**Dolutegravir / abacavir / lamivudine fixed-dose combination for HIV**

**Product name:** Triumeq®

Dolutegravir / abacavir / lamivudine 50 / 600 / 300 mg fixed-dose combination

**Class:** Antivirals for treatment of HIV infections; ATC code: J05AR13

**Approval:** EMA

**Use:** Treatment of Human Immunodeficiency Virus (HIV)-infected adults and adolescents above 12 years of age weighing at least 40 kg.

**Benefits:** Potent antiretroviral response, with a high barrier to resistance in a once-daily, single pill regimen

**Safety information:** Should not be used in patients known to carry the HLA-B*5701 allele (a genetic marker indicating a high risk of abacavir hypersensitivity)
► EMA/CHMP Summary of opinion, 26 June 2014.

**Tedizolid phosphate for skin infections**

**Product name:** Sivextro®

**Class:** Oxazolidinone antibacterial

**Approval:** FDA (expedited review under Qualified Infectious Disease Product designation)

**Use:** Treatment of acute bacterial skin and skin structure infections in adults. The product is available for intravenous and oral use.

**Benefits:** Additional treatment options against skin infections caused by *Staphylococcus aureus* (including methicillin-resistant and -susceptible strains), various *Streptococcus* species, and *Enterococcus faecalis*.

**Safety information:** The safety and efficacy of tedizolid phosphate have not been evaluated in patients with decreased levels of white blood cells (neutropenia). Alternative therapies should be considered in these patients.
► FDA News release, June 20, 2014.

**Oritavancin for skin infections**

**Product name:** Orbactiv®

**Class:** Glycopeptide antibacterial; ATC code: J01XA05

**Approval:** FDA; priority review due to Qualified Infectious Disease Product (QIDP) designation

**Use:** Intravenous treatment of acute bacterial skin and skin structure infections caused by certain susceptible bacteria, including *Staphylococcus aureus* (both methicillin-susceptible and methicillin-resistant strains), various *Streptococcus* species and *Enterococcus faecalis*.

**Benefits:** Additional treatment option for the above-mentioned, serious infections.

**Safety information:** The product information includes a warning about interference of oritavancin with coagulation tests and interaction with warfarin.
► FDA News release, 6 August 2014.

**Belinostat for peripheral T-cell lymphoma**

**Product name:** Beleodaq®

**Class:** Antineoplastic agent

**Approval:** FDA (accelerated approval; orphan designation)

**Use:** Treatment of peripheral T-cell lymphoma, a rare and fast-growing type of non-Hodgkin lymphoma.

**Benefits:** Additional treatment option for patients who had relapses or did not respond to previous treatment.
► FDA News release, 3 July 2014.

**Ibrutinib for blood cancers**

**Product name:** Imbruvica®

**Class:** Antineoplastic agent; ATC code: L01XE27

**Approval:** FDA (new indication, breakthrough therapy); EMA (orphan medicine)

**Uses:** Treatment of chronic lymphocytic leukaemia in patients with a specific genetic mutation; treatment of relapsed or refractory mantle cell lymphoma
Benefits: Longer progression-free survival and overall survival periods.

**Idelalisib for blood cancers**

**Product name:** Zydelig®
**Class:** Antineoplastic agent; ATC Code: L01XX47
**Approval:** FDA (orphan designation, breakthrough therapy); EMA
**Uses:** Treatment of blood cancers, including relapsed chronic lymphocytic leukaemia, in combination with rituximab; refractory follicular lymphoma; and relapsed small lymphocytic lymphoma after at least two systemic therapies
**Benefits:** Longer progression-free survival in chronic lymphocytic leukaemia; improved response rate and response duration in follicular lymphoma.
**Safety information:** Risk of fatal and serious toxicities including liver toxicity, diarrhoea and colon inflammation, lung inflammation and intestinal perforation. The FDA approved the product with a Boxed Warning and with a Risk Evaluation and Mitigation Strategy; the EMA required the implementation of a pharmacovigilance plan.

**Bevacizumab for late-stage cervical cancer**

**Product name:** Avastin®
**Class:** Antiangiogenic agent, monoclonal antibody; ATC code: L01XC07
**Approval:** FDA, new indication (priority review)
**Use:** Treatment of persistent, recurrent or late-stage (metastatic) cervical cancer in combination with other medicines.
**Benefits:** Increased overall survival time, compared with chemotherapy alone.
**Safety information:** Bevacizumab can cause perforations of the gastrointestinal tract or abnormal openings between the gastrointestinal tract and vagina.
► FDA News release, 14 August 2014.

**Suvorexant for insomnia**

**Product name:** Belsomra®
**Class:** Orexin receptor antagonist (first-in-class)
**Approval:** FDA
**Use:** Treatment of insomnia
**Benefits:** Effective compared to placebo.
**Safety information:** Patients using the highest strength (20 mg) should be cautioned against next-day driving or activities requiring full mental alertness. Lower doses can also impair next-day alertness as there is individual variation in sensitivity to the drug. People can be impaired even when they feel fully awake. The product will be dispensed with an FDA-approved patient medication guide. It has been classified as a controlled substance because it can be abused or lead to dependence.
► FDA News release, 13 August 2014.

**Olodaterol for chronic obstructive pulmonary disease (COPD)**

**Product name:** Striverdi Respimat® Inhalation spray
**Class:** Long-acting beta-adrenergic agonist (LABA); ATC code: R03AC19
**Approval:** FDA
**Use:** Long-term treatment of COPD, including chronic bronchitis and/or emphysema
**Benefits:** Additional long-term maintenance treatment option for patients with chronic airway obstruction
**Safety information:** Olodaterol carries a Boxed Warning stating that LABAs increase the risk of asthma-related death. Its safety and effectiveness in people with asthma has not been established, and it is not approved to treat asthma. It should not be used to treat acute breathing problems, or in patients with acutely deteriorating COPD. Serious potential side effects include paradoxical bronchospasm and cardiovascular effects. The FDA approved the product with a patient medication guide.
**Technetium 99m tilmanocept for diagnosis in cancers**

**Product name:** Lymphoseek®

**Class:** Diagnostic radiopharmaceutical agent; 
ATC code: V09IA09

**Approval:** FDA (new indication)
EMA (initial authorization)

**Use:** FDA: To guide lymph node biopsy in the head and neck region in patients with squamous cell carcinoma. (Approved in 2013 to assist in the localization of lymph nodes draining a primary tumour in patients with breast cancer or melanoma.)

EMA: Imaging and intraoperative detection of sentinel lymph nodes draining a primary tumour in adult patients with breast cancer, melanoma, or localised squamous cell carcinoma of the oral cavity. External imaging and intraoperative evaluation may be performed using a gamma detection device.

**Benefits:** Ability to detect tumour-draining sentinel nodes, allowing for the option of more limited lymph node surgery in patients with lymph nodes that are found to be negative for cancer.

- FDA News release, 13 June 2014.

---

**Flutemetamol (18F) for diagnosis of Alzheimer’s disease**

**Product name:** Vizamyl®

**Class:** Diagnostic radiopharmaceutical agent; 
ATC code: V09AX04

**Approval:** EMA

**Use:** Diagnosis of patients investigated for Alzheimer’s disease. Injected flutemetamol binds to amyloid neuritic plaques in the human brain which can then be seen by positron emitting tomography (PET). The product should be prescribed by clinicians experienced in the clinical management of neurodegenerative disorders.

**Benefits:** Flutemetamol can help detect with a high accuracy the beta-amyloid deposition, and therefore contribute valuable additional diagnostic information in Alzheimer’s disease.

- EMA/CHMP Summary of opinion, 26 June 2014.

---

**Withdrawn applications**

<table>
<thead>
<tr>
<th>Submission</th>
<th>Applicant’s reason for withdrawal</th>
<th>Reviewing authority reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faldaprevir for treatment of hepatitis C Submitted to EMA (orphan designation)</td>
<td>Since several new treatments for hepatitis C had become available after the application was first made, there was no longer an unmet medical need for such a medicine.</td>
<td>EMA. Questions and answers on the withdrawal of the marketing authorisation application for Faldaprevir Boehringer Ingelheim (faldaprevir). 27 June 2014.</td>
</tr>
<tr>
<td>Vintafolide, with diagnostic medicines etarfolatide and folic acid, for treatment of ovarian cancer Submitted to EMA (orphan designation)</td>
<td>The preliminary data from the study could not confirm the benefit of vintafolatide in ovarian cancer patients, and confirmatory data cannot be provided since the study has been terminated.</td>
<td>EMA. Questions and answers on the withdrawal of the marketing authorisation application for Vynfinit (vintafolide). 23 May 2014.</td>
</tr>
</tbody>
</table>
WHO panels advise on medical interventions in Ebola outbreak

Geneva – A WHO-convened panel has reached consensus that in the particular circumstances of the severe Ebola outbreak in West Africa, with no treatment or vaccine yet having been evaluated in human beings, it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects to save the lives of patients and to curb the epidemic. The panel agreed that ethical criteria – including transparency, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity and community involvement – must guide such interventions, and that there is a moral obligation to collect and share all data generated, and to evaluate these interventions in the best possible clinical trials under the circumstances.

At the margins of the 16th WHO International Conference of Drug Regulatory Authorities (ICDRA) held in August 2014, members of an interim International Coalition of Medicines Regulatory Authorities (ICMRA) pledged to cooperate among themselves and with WHO on fast access to investigational treatments for patients most in need, and on access to safe and efficacious medicines in the future so that public health authorities in affected countries can respond effectively to outbreaks.

On 4–5 September, WHO brought together technical experts to discuss potential Ebola therapies and vaccines. The group identified some promising investigational treatments (although supplies will be limited for some time to come) and identified two advanced vaccines for accelerated development. If proven safe, a vaccine could be available in November 2014 for priority use in health-care workers. The group stressed that effective clinical care, rigorous infection prevention and control, careful contact tracing and follow-up, effective risk communication and social mobilization remain crucial to end the outbreaks.

On 18 September, in its first emergency meeting on a public health crisis, the UN Security Council declared the outbreak a threat to peace and security. The UN Secretary-General announced the deployment of a new emergency health mission to be known as the UN Mission for Ebola Emergency Response (UNMEER). The Ebola outbreak confirmed in West Africa in March 2014 is the largest, most severe and most complex in history.

►WHO Statement, 12 August 2014.
EMA News, 4 September 2014.
WHO Statement, 5 September 2014.
UN News, 18 September 2014.

1 Members of the interim ICMRA Management Committee include: Therapeutic Goods Administration (TGA), Australia; National Health Surveillance (ANVISA), Brazil; Health Products and Food Branch, Health Canada (HPFB-HC), Canada; China Food and Drug Administration (CFDA), China; European Medicines Agency (EMA); European Commission - Directorate General for Health and Consumers (DG - SANCO); Health Product Regulatory Authority (HPRA), Ireland; Italian Medicines Agency (AIFA), Italy; Ministry of Health, Labour and Welfare (MHLW), and the Pharmaceuticals and Medical Devices Agency (PMDA), Japan; Medicines Evaluation Board (MEB), Netherlands; Health Sciences Authority (HSA), Singapore; Medicines Control Council (MCC), South Africa; Medicines and Healthcare Products Regulatory Agency (MHRA), United Kingdom; Food and Drug Administration (FDA), United States.
Public health

UNAIDS report on HIV treatment coverage
Geneva – The newly published UNAIDS “Gap report” highlights the need for a smart scale-up to bring antiretroviral treatment to all who need it.

According to the report, 19 million of the 35 million people living with HIV today do not know that they have the virus. An estimated 14 million people were on ARV treatment at the end of July 2014, and new analyses show that the rate of new infections slows down with increasing treatment coverage. If the scale-up can be accelerated to reach all people in need of ARVs by 2020, the world could be on track to end the epidemic by 2030.

Closing the gap will require research and innovation, combined with protective laws that promote freedom and equality for all people. This will create space for tailored solutions to address the complex, varied epidemics and prevailing stigma within countries and communities.


Access to antiretroviral medicines in low- and middle-income countries
Geneva – WHO has released a report that examines global trends in antiretroviral (ARV) prices and assesses how WHO treatment guidelines have influenced the uptake of different ARV formulations. It describes constraints limiting the use of second-line, third-line and paediatric treatments, and explores how ARV quality can be secured and in-country distribution can be improved.

This publication complements an earlier WHO report, published in May 2014, on access to ARVs in middle-income countries in light of regulatory, pricing and intellectual property information.


UK studies show safety and effectiveness of whooping cough vaccination in pregnant women
United Kingdom – Young infants are at the highest risk of severe complications and death from whooping cough, as babies do not complete vaccination until they are four months old. The UK Department of Health had announced a temporary vaccination programme for pregnant women in October 2012 in response to a national whooping cough outbreak that had led to several infant deaths.

New research has shown that vaccinating pregnant women against whooping cough has been highly effective in protecting young infants from this potentially fatal disease. These findings are supplemented by the first large study of the whooping cough vaccine safety in pregnancy, conducted by the MHRA. The programme will now be continued for a further five years.


Swissmedic and Health Canada join ICH Steering Committee

Minneapolis – The International Conference on Harmonisation (ICH) Steering Committee and its Expert Working Groups met in Minneapolis, USA on 31 May – 5 June 2014. At the meeting the ICH Steering Committee decided to include the Swiss Agency for Therapeutic Products Swissmedic and the Canadian Health Authority Health Canada as ICH Steering Committee members.

The membership was granted in recognition of the two organizations’ historical involvement and commitment to ICH, and started with immediate effect. The new roles of Swissmedic and Health Canada conform to a broader range of evolving ICH membership and governance reforms.

► ICH Press release, 8 July 2014.

Novartis transfers tuberculosis drug development to Global TB Alliance

Basel – Novartis has signed an exclusive worldwide licensing agreement with the Global Alliance for TB Drug Development (TB Alliance) for new anti-tuberculosis compounds discovered at the Novartis Institutes for Tropical Diseases (NITD). TB Alliance will take financial and operational responsibility for continued research, development, approval and distribution of the compounds, including a novel class of drugs called indolcarboxamides that are active against drug-sensitive and multi-resistant strains of tuberculosis.

TB Alliance is a not-for-profit organization with the mission of developing better, faster and affordable treatments for tuberculosis. It was launched in October 2000 at the International Conference on Health Research for Development in Thailand.

► TB Alliance News release, 19 August 2014.

Who matters

Why we need an independent, impartial WHO

An article in the BMJ warns that WHO’s stewardship to protect the health of all is weakened as the Organization lacks a guaranteed budget to perform its vital normative functions.

WHO’s core budget has dwindled as the US and other countries have adopted zero nominal growth policies for their UN agencies core contributions – a decline in real terms – and many Member States are in arrears with payments. Today, 80% of WHO’s total budget are voluntary contributions from the public and private sector, meaning that the donor has control on how the funds are spent. Often this funding is given to disease-specific causes, and often these are disconnected from the global burden of diseases.

The authors emphasize that WHO is the only international agency that can broker global rules in the interest of public health. As new challenges arise that threaten health security across the world, assured funding to preserve the independence and neutrality of WHO becomes even more important.

WHO Drug Information Vol. 28, No. 3, 2014

The International Pharmacopoeia – Fourth Supplement published
WHO has published the Fourth Supplement of The International Pharmacopoeia, which provides specifications and test methods for reference or adaptation by any WHO Member State.

The Fourth Supplement introduces new or revised texts for eight monographs on active pharmaceutical ingredients, 15 finished product monographs, one general monograph, three methods of analysis and three supplementary information texts. WHO gratefully acknowledges the support from a wide range of experts and institutions in developing these texts.

Some highlights in this supplement include: (1) a new monograph on capreomycin sulfate with related substances test methods and limits that will help manufacturers to limit the toxicity of their capreomycin-containing products; (2) A revised monograph on artemisinin, enabling manufacturers to evaluate its quality using the same analytical methods as for artemisinin when used as a starting material; (3) a clarification note on dissolution test requirements for chewable tablets, considering that these may be swallowed whole; and (4) a new chapter on reference substances and reference spectra, with explanations of concepts and hands-on advice.


WHO-ISoP core elements of teaching pharmacovigilance
Pharmacovigilance experts from WHO Member States, the International Society of Pharmacovigilance (ISoP) and its Education and Training Project (ETP), have jointly developed a comprehensive and balanced pharmacovigilance curriculum.

The importance of pharmacovigilance for safe medicines and their safe use are gaining recognition, particularly in countries where highly effective but potentially harmful chemical medicines have come to replace traditional treatments.

To help orientate pharmacovigilance education and training amidst an abundance of guidelines and publications, the curriculum provides an inventory and overview of the scope of pharmacovigilance, including relatively new topics such as pharmacogenomics, consumer reporting of adverse drug reactions, risk management and WHO-led international projects. While it is not intended as ready-for-use teaching material or a course description, it reflects the current status of the rapidly evolving science of pharmacovigilance and provides a rich and valuable bibliography.

Consultation documents

Medicines quality assurance texts

General guidance on “hold-time” studies

This is a revised draft proposal for a new medicines quality assurance guideline (Working document QAS/13.521/Rev.3, August 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; Dr Sabine Kopp, kopps@who.int and Ms Marie Gaspard, gaspardm@who.int.

Contents

1. Introduction and background
2. Glossary
3. Scope
4. Aspects to be considered

1. Introduction and background

Manufacturers should ensure that the products that they manufacture are safe, effective and of the quality required for their intended use. Products should be consistently manufactured to the quality standards appropriate to their intended use and as required by the marketing authorization. Systems should ensure that pharmaceutical products are produced according to validated processes and to defined procedures. Manufacturing processes should be shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications.

Arrangements should exist to ensure that the dispensed raw materials and packaging materials, intermediate products, bulk and finished products are stored under appropriate conditions. Storage should not have any significant negative effect on the processing, stability, safety, efficacy or quality of the materials, intermediate products and bulk products prior to final packing. Good manufacturing practices (GMP) require that a maximum acceptable holding period should be established to ensure that intermediates and bulk product can be held, pending the next processing step, without any significant adverse effect to the quality of the material. Such a holding period should be underwritten by data, but need not be extended to find the edge of failure.

2. Glossary

Bulk product
Any pharmaceutical product which has completed all processing stages up to, but not including, final packaging.

Intermediate
Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.
3. **Scope**

This guideline focuses primarily on aspects that should be considered in the design of the hold-time studies during the manufacture of solid dosage forms. Many of the principles herein also apply to other dosage forms such as liquids, creams, and ointments. This guideline does not cover aspects for hold times in cleaning validation or the manufacturing of active pharmaceutical ingredients (APIs).

This guideline is intended as a basic guide for use by pharmaceutical manufacturers and GMP inspectors. This document does not intend to prescribe a process for establishing hold times, but reflects aspects that should be considered in the design of the hold-time study.

Manufacturers should gather scientific and justifiable data to demonstrate that the dispensed raw materials and packaging materials, intermediate and bulk products:

- remain of appropriate quality before processing to the next stage;
- meet the acceptance criteria and release specification for the finished product.

**4. Aspects to be considered**

Hold time can be considered as the established time period for which materials (dispensed raw materials, intermediates and bulk dosage form awaiting final packaging) may be held under specified conditions and will remain within the defined specifications.

Data to justify the hold time can be collected, but not limited to:

- during development on pilot-scale batches,
- during scale up,
- during process validation, or
- as part of an investigation of a deviation that occurred during manufacture.

Hold-time studies establish the time limits for holding the materials at different stages of production to ensure that the quality of the product does not deteriorate significantly during the hold time. The design of the study should reflect the holding time at each stage. Hold times should normally be determined prior to marketing of a product and following any significant changes in processes, equipment, starting and packaging materials and represent actual processing. Hold time studies should be included during process validation (Ref: Process validation guideline).

Manufacturers may use a flow chart to review the manufacturing procedure of a product and then break up the critical stages of manufacturing process on the basis of time duration required for the particular storage and processing stages, typical pauses in the manufacturing campaign, and the potential impact of storage with reference to environmental and storage conditions. An example for a flow chart is given below.

For example, for oral tablets that are coated the following stages may be considered:

- binder preparation to granulation – consider the granulate;
- wet granulation to drying – the dried granulate;
- dried granules to lubrication/blending – the lubricated blend;
- blend to compression;
- compression to coating – the tablet cores;
- coating solution to preparation – the coating solution;
- coating to packing – consider the bulk coated tablets;
- coating to packing in bulk or FDF;
- packing in bulk to FDF.
A written protocol, procedure or programme should be followed which includes the activities to be performed, test parameters and acceptance criteria appropriate to the material or product under test. The protocol and report should generally include the following: a title; reference number; version; date; objective; scope; responsibility; procedure; description of the material/product; sample quantities; sampling method and criteria; acceptance limits; frequency for sampling; sampling locations; pooling of samples; storage conditions; type of container; methods of analysis; results; conclusion; recommendation; signatures and dates. Acceptance criteria are typically more stringent than registered specifications to provide assurance that the material is well within control.

When setting the specifications any known stability trends will need to be taken into account.

For certain products microbiological aspects should also be considered and included where appropriate.

Typically one or more batches of a material, intermediate or product can be used for determining hold times. A risk-based approach can be used to determine the appropriate number of batches, considering inter alia the characteristics of the materials. A representative sample of the batch of material or product subjected to the hold-time study should be held for the defined hold period. The maximum hold period for each category of material should be established on the basis of the study by keeping the material in either
the original or simulated container used in production. The containers used in which hold-
time samples are stored should be the same pack as used in production unless the pack is
exceptionally large, in which case one that is equivalent (same material of construction and
closure system to the production packaging system) may be used. Reducing the size of
container when necessary for testing holding time, should be justified. Where head space
is important the hold-time samples should represent the maximum possible head space
(worst-case scenario) to bulk stored in manufacturing/quarantine. The sample storage
environmental conditions should be same as that of the quarantine area/manufacture
stage. A sampling plan should be established and followed for taking samples for testing
at the different intervals. The required sample amount should be calculated based on the
batch size, the intervals and tests to be performed. Results should be compared with the
initial baseline data of the control sample. Samples may be pooled for analysis where
appropriate, e.g. when the analysis of a composite sample will not miss issues expected in
the variation of the product.

Where appropriate, statistical analysis of the data generated should be performed to
identify trends and to justify the limits and hold time set.

Batches of finished products made from intermediates or bulk products and subjected to
a hold-time study should be considered for long-term stability testing if data show adverse
trending or shifting patterns during the intermediate time points up to the end of the shelf-
life. The shelf-life of the product – irrespective of hold times – should be measured from
the time the active ingredients are mixed with other ingredients. Normally intermediate
and bulk products should not be stored beyond the established hold time. All testing of
bulk intermediates and product should be performed using validated stability-indicating
methods.

The following table provides examples of stages and tests that may be considered.

Table: Examples of stages and tests that may be considered, based on risk
assessment and specific product needs

<table>
<thead>
<tr>
<th>Stage</th>
<th>Test to be carried out as per specification</th>
<th>Study time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binder preparation</td>
<td>Microbial test</td>
<td>Initial, 2hrs, 5hrs, 8hrs. In case of starch: initial, 2hrs, 5hrs</td>
</tr>
<tr>
<td>Solution prepared (including granulation pastes, coating solution and coating suspension)</td>
<td>Physical appearance, Specific gravity, Viscosity, Sedimentation, pH, Microbial test</td>
<td>Initial, 12, 24, 36, 48, 60, 72 hours</td>
</tr>
<tr>
<td>Granule</td>
<td>Description, Assay, Related substances, Loss on drying, Water content, Particle size distribution, Bulk density, Tap density, Angle of repose</td>
<td>Initial, 30th day, 45th day</td>
</tr>
<tr>
<td>Blend</td>
<td>Microbial test, Loss on drying, Blend uniformity, Particle size, Bulk/Tapped density</td>
<td>Initial, 30th day, 45th day</td>
</tr>
</tbody>
</table>

Continued
### Consultation documents

#### Continued

<table>
<thead>
<tr>
<th>Stage</th>
<th>Test to be carried out as per specification</th>
<th>Study time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core tablets – uncoated (in bulk container)</td>
<td>Description, Hardness, Thickness, Friability, Disintegration, Dissolution or Dissolution profile, Assay, Degradation products/ related substance, Uniformity of dosage units, Microbial test.</td>
<td>Initial, 30\textsuperscript{th} day, 60\textsuperscript{th} day &amp; 90\textsuperscript{th} day</td>
</tr>
<tr>
<td>Coated tablets (in bulk container)</td>
<td>Description, Hardness, Thickness, Friability, Disintegration, Dissolution or Dissolution profile, Assay, Degradation products/ related substance, Uniformity of dosage units, Moisture content, Microbial test.</td>
<td>Initial, 30\textsuperscript{th} day, 60\textsuperscript{th} day &amp; 90\textsuperscript{th} day</td>
</tr>
</tbody>
</table>

***
Good review practices guidelines for regulatory authorities

A revised draft guidance text on good review practices for medical products was endorsed by the Regulatory Harmonization Steering Committee (RHSC) of the Asia-Pacific Economic Cooperation (APEC) at its meeting in China in August 2014 for submission to WHO. The document incorporates outcomes and comments from a parallel consultation process through both the WHO Expert Committees on Specifications for Pharmaceutical Preparations and on Biological Standardization.

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; Dr Sabine Kopp, kopps@who.int and Ms Marie Gaspard, gaspadrm@who.int.

Due to space limitations it was not possible to include the full proposed text in this issue of WHO Drug Information. An outline is reproduced below.

1. Introduction
   1.1 Document objective
   The objective of the document is to provide high level guidance on good review practice (GRevP) principles and processes, for use across a range of regulatory authority (RA) maturities. It is not intended to provide detailed instruction on how to conduct a scientific review.
   This document is envisioned as one building block in a set of tools and is sufficiently expandable to accommodate additional annexes or ancillary documents in the future.
   1.2 Context
   1.3 Definitions
   1.4 Scope
2. Principles of a good review
3. Managing the review
   3.1 Project management
   3.2 Quality management
   3.3 Standard operating procedures
   3.4 Review process stages
4. Communications
   4.1 Intra-agency
   4.2 Interagency
   4.3 With applicants
   4.4 With external experts
   4.5 With the public
5. Review personnel
   5.1 Reviewer expertise, competencies and training
   5.2 Critical thinking
6. Conducting the review
   6.1 Key elements in defining a review strategy
   6.2 Applying the review strategy
7. Glossary
8. References

Pyranteli embonas
Pyrantel embonate

This is a draft proposal for The International Pharmacopoeia (Working document QAS/14.589, June 2014).

The working document with line numbers and tracked changes is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

[Note from the Secretariat. It is proposed to revise the monograph on Pyrantel embonate.]

[Note from the editor. In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and delete in the working document available at the above-mentioned web address.]

Molecular formula. $\text{C}_{11}\text{H}_{14}\text{N}_2\text{S}_2\text{C}_{23}\text{H}_{16}\text{O}_6$

Relative molecular mass. 594.7

Graphic formula.


Other name. Pyrantel pamoate.

Description. A pale yellow or yellow powder.

Solubility. Practically insoluble in water and methanol R; soluble in dimethyl sulfoxide R; slightly soluble in dimethylformamide R.

Category. Anthelmintic.

Storage. Pyrantel embonate should be kept in a well-closed container, protected from light.

Requirements

Definition. Pyrantel embonate contains not less than 98.0 and not more than 102.0 of $\text{C}_{11}\text{H}_{14}\text{N}_2\text{S}_2\text{C}_{23}\text{H}_{16}\text{O}_6$, calculated with reference to the dried substance.
Identity tests

- Either tests A alone or tests B and C may be applied.
  
  A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from pyrantel embonate RS or with the reference spectrum of pyrantel embonate.
  
  B. The absorption spectrum of a 13 μg/mL solution in methanol R, when observed between 230 nm and 360 nm, exhibits 2 maxima at about 288 nm and 300 nm. The ratio of the absorbance at 288 nm to that at 300 nm is about 1.0.
  
  C. See the test described under “Related substances”, Method A. The principal spots obtained with solution (1) correspond in position, appearance and intensity with those obtained with solution (3).

Chlorides. Dissolve 0.46 g of Pyrantel embonate in a mixture of 10 mL of nitric acid (~130 g/L) TS and 30 mL of water R. Heat on a water-bath for 5 min, allow to cool, dilute to 50 mL with water R, mix well and filter. Add 1 mL of nitric acid (~130 g/L) TS to 15 mL of the filtrate and proceed as described under 2.2.1 Limit test for chlorides; the chloride content is not more than 0.36 mg/g.

Sulfates. Dissolve 0.50 g of Pyrantel embonate in 2.5 mL of nitric acid (~130 g/L) TS and dilute to 30 mL with water R. Heat on a water-bath for 5 min, shake for 2 min, cool and filter and proceed as described under 2.2.2 Limit test for sulfates; the sulfate content is not more than 1 mg/g.

Iron. Ignite 0.66 g of Pyrantel embonate at 800 ± 50 °C for 2 h. Cool and dissolve the residue in 2.5 mL of hydrochloric acid (~70 g/L) with gentle heating for 10 min. Cool and dilute to 40 mL with water R and proceed as described under 2.2.4 Limit test for iron; not more than 75 μg/g.

Sulfated ash. Not more than 1.0 mg/g.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to Method A; not more than 10 μg/g.

Loss on drying. Dry at 60 °C under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) for 3 hours; it loses not more than 10 mg/g.

Related substances

Carry out the operations in subdued light and without any prolonged interruptions, preferably using low-actinic glassware.

- Either method A or B may be applied.
  
  A. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 3 volumes of ethyl acetate R, 1 volume of water R and 1 volume of glacial acetic acid R as the mobile phase.

  Prepare the following solutions. For solution (1) dissolve about 100 mg of Pyrantel embonate in 10.0 mL dimethylformamide R (1). For solution (2) dilute 1.0 mL of solution (1) to 100 mL with dimethylformamide R. For solution (3) use 10 mg of pyrantel embonate RS per mL dimethylformamide R. For solution (4) expose a quantity of solution (3) under 2000 lx illumination for 24 hours. In case a suitable device to provide the requested illuminance is not available use 10 mg of pyrantel embonate impurity A RS and 2 mg pyrantel embonate RS per mL dimethylformamide R for solution (4).
Apply separately to the plate 5 μL of each of the solutions (1), (2), (3) and (4).

After application allow the spots to dry for 15 minutes in a current of air. Develop over a path of 12 cm. After removing the plate from the chromatographic chamber allow it to dry for 10 minutes in a current of air. Examine the chromatogram in ultraviolet light (254 nm).

Pyrantel and related substances have the following Rf values: impurity A about 0.2; pyrantel about 0.3; embonic acid about 0.9. The test is not valid unless the chromatogram obtained with solution (4) exhibits three well separated spots.

In the chromatogram obtained with solution (1) any spot, other than the two principal spots, is not more intense than the pyrantel spot in the chromatogram obtained with solution (2) (1.0%). Disregard any spot remaining at the point of application.

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with high purity base particles of silica gel for chromatography R (5 μm)1.

As the mobile phase use a mixture of 92.8 volumes of acetonitrile R and 7.2 volumes of a solvent mixture composed of 5 volumes of glacial acetic R, 5 volumes of water R and 2 volumes of diethylamine R.

Prepare the following solutions. For solution (1) transfer about 72 mg of Pyrantel embonate, accurately weighed, to a 100 mL volumetric flask. Add 7 mL of a mixture composed of 5 volumes of glacial acetic R, 5 volumes of water R and 2 volumes of diethylamine R. Shake and dilute to volume with acetonitrile R, mix and filter. For solution (2), dilute 1.0 mL of the solution (1) to 100.0 mL with mobile phase. For solution (3) expose 10 mL of solution (1) under 2000 lx illumination for 24 hours. In case a suitable device to provide the requested illuminance is not available transfer 10 mg of pyrantel embonate impurity A RS to a 10.0 mL flask, add 8 mL of solution (1) and make up to volume with dimethylformamide R to obtain solution (3).

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 288 nm.

Inject separately 20 μL each of solution (1), (2) and (3) and record the chromatograms for 4 times the retention time of pyrantel.

In the chromatogram obtained with solution (3) the following peaks are eluted at the following relative retention with reference to pyrantel (retention time about 14 minutes): embonic acid about 0.5; impurity A about 1.3. The test is not valid unless the resolution factor between the pyrantel peak and the impurity A peak is at least 4.0.

In the chromatogram obtained with solution (1) the area of any impurity peak is not greater than the area of the pyrantel peak obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak obtained with solution (2) (0.1%).

**Assay**

Perform the assay in subdued light and without any prolonged interruptions, preferably using low-actinic glassware.

---

1 Shim-pack HRS-SIL column (25 cm × 4.6 mm, 5 μm) has been found suitable.
Dissolve about 0.450 g of Pyrantel embonate, accurately weighed, in 10 mL of acetic anhydride R and 50 mL of glacial acetic acid R. Heat at 50 °C and stir for 10 minutes. Allow to cool and titrate the suspension with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A, determining the end-point potentiometrically. Carry out a blank titration.

Each ml of perchloric acid (0.1 mol/L) VS is equivalent to 59.47 mg of pyrantel embonate C_{11}H_{14}N_2S.C_{23}H_{16}O_6.

### Impurities

A. 1-methyl-2-[(1E)-2-(thiophen-2-yl)ethenyl]-1,4,5,6-tetrahydropyrimidine.

***
Pyranteli compressi
Pyrantel tablets

This is a draft proposal for The International Pharmacopoeia (Working document QAS/14.588, June 2014).

The working document with line numbers and tracked changes is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidt@who.int.

[Note from the Secretariat. It is proposed to revise the monograph on Pyrantel embonate tablets.

[Note from the editor. In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and delete in the working document available at the above-mentioned web address.]

Category. Anthelminthic.

Storage. Pyrantel tablets should be kept in a tight, lightly-closed container, protected from light.

Labelling. The designation on the container of Pyrantel tablets should state that the active ingredient is in the embonate form, and the quantity should be indicated in terms of equivalent amount of pyrantel.

Additional information. Strength in the current WHO Model List of Essential Medicines: 250 mg of pyrantel (as embonate or pamoate).

Requirements

Comply with the monograph for Tablets.

Definition. Pyrantel tablets contain not less than 90.0% and not more than 110.0% of the amount of pyrantel \((C_{11}H_{14}N_2S)\) stated on the label.

Identity tests

• Either test A alone, or any two of tests B, C and D may be applied.

To a quantity of the powdered tablets containing the equivalent of about 20 mg of pyrantel add a mixture of 10 mL of dichloromethane R, 10 mL of methanol R and about 1 mL of ammonia \((\sim 260g/L)\) TS, shake and filter. Evaporate the filtrate to dryness on a water-bath, dissolve in a small volume of methanol R (about 3 mL) by heating on a water-bath and then allowing the solution to cool. Separate the crystals, dry at 80 °C for 2 hours and use the dried crystals for the “Identity tests” A and C.

A. Carry out the examination with the dried crystals as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from pyrantel embonate RS or with the reference spectrum of pyrantel embonate.

B. See the test described below under “Related substances”, Method A. The principal spots obtained with solution (1) correspond in position, appearance and intensity with those obtained with solution (3).
C. The absorption spectrum (1.6) of a 13 \( \mu g/mL \) solution of the dried crystals in methanol R, when observed between 230 nm and 360 nm, exhibits 2 maxima at about 288 nm and 300 nm. The ratio of the absorbance at 288 nm to that at 300 nm is about 1.0.D. See the test described under “Assay”. The retention times of the principal peaks in the chromatogram obtained from solution (1) are similar to those obtained from solution (2).

D. See the test described under “Assay”. The retention times of the principal peaks in the chromatogram obtained from solution (1) are similar to those obtained from solution (2).

### Dissolution

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using as the dissolution medium, 900 mL of a solution prepared by dissolving 1.0 g of sodium dodecyl sulphate R and 7 mL hydrochloric acid (~420g/L) TS in 1000 mL of water. Rotate the paddle at 75 revolutions per minute. At 60 minutes withdraw a sample of 10 mL of the medium through an in-line filter. Transfer 1.0 mL of the clear filtrate to a 50 mL volumetric flask and dilute to volume with hydrochloric acid/methanol (0.1 mol/L) VS (solution (1)). For solution (2) transfer about 20 mg of pyrantel embonate RS (equivalent to about 7.0 mg of pyrantel), accurately weighed, into a 25 mL volumetric flask. Add about 10 mL of dimethylformamide R, shake to dissolve and dilute to volume with hydrochloric acid/methanol (0.1 mol/L) VS. Transfer 1.0 mL of this solution to a 50 mL volumetric flask and dilute to volume with hydrochloric acid/methanol (0.1 mol/L) VS. Measure the absorbance (1.6) of the samples at a wavelength of 316 nm, using hydrochloric acid/methanol (0.1 mol/L) VS as the blank.

For each of the tablets tested calculate the total amount of pyrantel (C\(_{11}\)H\(_{14}\)N\(_2\)S) in the medium from the absorbances obtained using the declared content of C\(_{11}\)H\(_{14}\)N\(_2\)S,C\(_{23}\)H\(_{16}\)O\(_6\) in pyrantel embonate RS. Each mg of pyrantel embonate C\(_{11}\)H\(_{14}\)N\(_2\)S,C\(_{23}\)H\(_{16}\)O\(_6\), is equivalent to 0.3469 mg of pyrantel C\(_{11}\)H\(_{14}\)N\(_2\)S. Use the requirements as described under 5.5 Dissolution test for solid oral dosage forms. Acceptance criteria to evaluate the results: the amount in solution is not less than 70% (Q) of the amount declared on the label.

### Related substances

Carry out the operations in subdued light and without any prolonged interruptions, preferably using low-actinic glassware.

- Either method A or B may be applied.

A. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 3 volumes of ethyl acetate R, 1 volume of water R and 1 volume of glacial acetic acid R as the mobile phase.

Prepare the following solutions. For solution (1) add to a quantity of the powdered tablets equivalent of about 35 mg of pyrantel a mixture of 10 mL of dichloromethane R, 10 mL of methanol R and about 1 mL of ammonia (~260 g/L) TS, shake and filter. Evaporate the filtrate to dryness on a water-bath and dissolve the dried residue in 10.0 mL dimethylformamide R. For solution (2) dilute 1.0 mL of solution (1) to 100 mL with dimethylformamide R. For solution (3) use 10 mg of pyrantel embonate RS (equivalent to about 3.5 mg of pyrantel) per mL dimethylformamide R. For solution (4) expose a quantity of solution (3) under 2000 l x illumination for 24 hours. In case a suitable device to provide the requested illuminance is not available use 10 mg of pyrantel embonate impurity A RS and 2 mg pyrantel embonate RS (equivalent to about 0.7 mg of pyrantel) per mL dimethylformamide R for solution (4).

Apply separately to the plate 5 \( \mu l \) of each of the solutions (1), (2), (3) and (4).

After application allow the spots to dry for 15 minutes in a current of air. Develop over a path of 12 cm. After removing the plate from the chromatographic chamber allow it
to dry in a current of air for 10 minutes. Examine the chromatogram in ultraviolet light (254 nm).

Pyrantel and related substances have the following Rf values: impurity A about 0.2; pyrantel about 0.3; embonic acid about 0.9. The test is not valid unless the chromatogram obtained with solution (4) exhibits three well-separated spots.

In the chromatogram obtained with solution (1) any spot, other than the two principal spots, is not more intense than the pyrantel spot in the chromatogram obtained with solution (2) (1.0%). Disregard any spot remaining at the point of application.

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets and transfer a quantity containing the equivalent of about 25 mg of pyrantel into a 100 mL volumetric flask. Add 7 mL of a mixture composed of 5 volumes of glacial acetic R, 5 volumes of water R and 2 volumes of diethylamine R. Shake and dilute to volume with acetonitrile R, mix and filter. For solution (2) dilute 1.0 mL of the solution (1) to 100.0 mL with mobile phase. For solution (3) expose 10 mL of solution (1) under 2000 l x illumination for 24 hours. In case a suitable device to provide the requested illuminance is not available transfer 10 mg of pyrantel embonate impurity A RS to a 10.0 mL flask, add 8 mL of solution (1) and make up to volume with dimethylformamide R to obtain solution (3).

Inject separately 20 μL each of solution (1), (2) and (3) and record the chromatograms for 4 times the retention time of pyrantel.

In the chromatogram obtained with solution (3) the following peaks are eluted at the following relative retention with reference to pyrantel (retention time about 14 minutes): embonic acid about 0.5; impurity A about 1.3. The test is not valid unless the resolution factor between the pyrantel peak and the impurity A peak is at least 4.0.

In the chromatogram obtained with solution (1): the area of any impurity peak is not greater than the area of the pyrantel peak obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak obtained with solution (2) (0.1%).

Assay

The operations described below must be carried out in subdued light and without any prolonged interruptions, preferably using low-actinic glassware.

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with high-purity base particles of silica gel for chromatography R (5 μm).1

As the mobile phase use a mixture of 92.8 volumes of acetonitrile R and 7.2 volumes of a solvent mixture composed of 5 volumes of glacial acetic R, 5 volumes of water R and 2 volumes of diethylamine R.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the tablets containing the equivalent of about 7.0 mg of pyrantel, accurately weighed, into a 50 mL volumetric flask. Add about 30 mL of mobile phase, shake for 10 minutes and dilute with mobile phase to volume, mix and filter. Transfer 2.0 mL of the clear filtrate to a 10 mL volumetric flask, dilute with mobile phase to volume and mix. For solution (2) prepare a solution of 0.40 mg of pyrantel embonate RS (equivalent to about 0.14 mg of pyrantel) per mL.

1 Shim-pack HRS-SIL column (25 cm×4.6 mm, 5 μm) has been found suitable
mobile phase. Transfer 2.0 mL of this solution to a 10 mL volumetric flask, dilute with mobile phase to volume, and mix to obtain a standard preparation having a known concentration of 80 μg of pyrantel embonate RS (equivalent to about 28 μg of pyrantel) per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 288 nm.

Inject separately 20 μL each of solution (1) and (2) and record the chromatograms.

In the chromatogram obtained with solution (2) the peak due to embonic acid is eluted at a relative retention time of about 0.5 with reference to pyrantel (retention time about 14 minutes).

Measure the areas of the peak responses due to pyrantel obtained in the chromatograms from solution (1) and solution (2), and calculate the content of pyrantel (C_{11}H_{14}N_{2}S) in the tablets, using the declared content of C_{11}H_{14}N_{2}SC_{23}H_{16}O_{6} in pyrantel embonate RS. Each mg of pyrantel embonate C_{11}H_{14}N_{2}SC_{23}H_{16}O_{6} is equivalent to 0.3469 mg of pyrantel C_{11}H_{14}N_{2}S.

**Impurites**

![Structural formula of impurity](image)

A. 1-methyl-2-[(1E)-2-(thiophen-2-yl)ethenyl]-1,4,5,6-tetrahydropyrimidine.

***

**Pyranteli compressi manducabili**

Pyrantel chewable tablets

This is a draft proposal for The International Pharmacopoeia (Working document QAS/14.587, June 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidt@who.int.

[Note from the Secretariat. It is proposed to revise the monograph on Pyrantel chewable tablets with a view to include a dissolution test.]

[Note from the editor. In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and delete in the working document available at the above-mentioned web address.]

**Category.** Anthelminthic.

**Storage.** Pyrantel chewable tablets should be kept in a tightly closed container, protected from light.

**Labelling.** The designation on the container of Pyrantel chewable tablets should state that the active ingredient is in the embonate form and the quantity should be indicated in terms of
equivalent amount of pyrantel and should state that the tablets may be chewed or swallowed whole.

**Additional information.** Strength in the current WHO Model list of essential medicines: 250 mg of pyrantel (as embonate or pamoate).

**Requirements**

Comply with the monograph for Tablets.

Definition. Pyrantel chewable tablets contain Pyrantel embonate in a suitable basis that may contain suitable flavouring agents. They contain not less than 90.0% and not more than 110.0% of the amount of pyrantel (C\textsubscript{11}H\textsubscript{14}N\textsubscript{2}S) stated on the label.

**Identity tests**

- Either tests A alone, or any two of tests B, C, D and E may be applied.

To a quantity of the powdered tablets containing the equivalent of about 20 mg of pyrantel add a mixture of 10 mL of dichloromethane R, 10 mL of methanol R and about 1 mL of ammonia (~260 g/L) TS, shake and filter. Evaporate the filtrate to dryness on a water-bath, dissolve in a small volume of methanol R (about 3 mL) by heating on a water-bath and then allowing the solution to cool. Separate the crystals, dry at 80 °C for 2 hours and use the dried crystals for "Identity tests A, C and D".

A. Carry out the examination with the dried crystals as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from pyrantel embonate RS or with the reference spectrum of pyrantel embonate.

B. See the test described under “Related substances”, Method A. The principal spots obtained with solution (1) correspond in position, appearance and intensity with those obtained with solution (3).

C. The absorption spectrum (1.6) of a 13 μg/mL solution of the dried crystals in methanol R, when observed between 230 nm and 360 nm, exhibits 2 maxima at about 288 nm and 300 nm. The ratio of the absorbance at about 288 nm to that at about 300 nm is about 1.0.

D. Dissolve about 5 mg of the dried crystals in 1 mL of hydrochloric acid (~70 g/L) TS and add 1 mL of formaldehyde/sulfuric acid TS; a violet-red colour is produced.

E. See the test described under “Assay”. The retention times of the principal peaks in the chromatogram obtained from solution (1) are similar to those obtained from solution (2).

**Dissolution**

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using as the dissolution medium, 900 mL of a solution prepared by dissolving 1.0 g of sodium dodecyl sulphate R and 7 mL hydrochloric acid (~420g/L) TS in 1000 mL of water. Rotate the paddle at 75 revolutions per minute. At 60 minutes withdraw a sample of 10 mL of the medium through an in-line filter. Transfer 1.0 mL of the clear filtrate to a 50 mL volumetric flask and dilute to volume with hydrochloric acid/methanol (0.1 mol/L) VS (solution (1)). For solution (2) transfer about 20 mg of pyrantel embonate RS (equivalent to about 7.0 mg of pyrantel), accurately weighed, into a 25 mL volumetric flask. Add about 10 mL of dimethylformamide R, shake to dissolve and dilute to volume with hydrochloric acid/methanol (0.1 mol/L) VS. Transfer 1.0 mL of this solution to a 50 mL volumetric flask and dilute to volume with hydrochloric acid/methanol (0.1 mol/L) VS . Measure the absorbance (1.6) of the samples at a wavelength of 316 nm, using hydrochloric acid/methanol (0.1 mol/L) VS as the blank.
For each of the tablets tested, calculate the total amount of pyrantel (C₁₁H₁₄N₂S) in the medium from the absorbances obtained using the declared content of C₁₁H₁₄N₂S₂C₂₃H₁₆O₆ in pyrantel embonate RS. Each mg of pyrantel embonate C₁₁H₆N₂S₂C₂₃H₁₆O₆ is equivalent to 0.3469 mg of pyrantel C₁₁H₁₄N₂S. Use the requirements as described under 5.5 Dissolution test for solid oral dosage forms, “Acceptance criteria” to evaluate the results: the amount in solution is not less than 65% (Q) of the amount declared on the label.

Related substances

Carry out the operations in subdued light and without any prolonged interruptions, preferably using low-actinic glasseware.

• Either method A or B may be applied.

A. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 3 volumes of ethyl acetate R, 1 volume of water R and 1 volume of glacial acetic acid R as the mobile phase.

Prepare the following solutions. For solution (1) add to a quantity of the powdered tablets equivalent of about 35 mg of pyrantel a mixture of 10 mL of dichloromethane R, 10 mL of methanol R and about 1 mL of ammonia (~260 g/L) TS, shake and filter. Evaporate the filtrate to dryness on a water-bath and dissolve the dried residue in 10.0 mL dimethylformamide R. For solution (2) dilute 1.0 mL of solution (1) to 100 mL with dimethylformamide R. For solution (3) use 10 mg of pyrantel embonate RS (equivalent to about 3.5 mg of pyrantel) per mL dimethylformamide R. For solution (4) expose a quantity of solution (3) under 2000 lx illumination for 24 hours. In case a suitable device to provide the requested illuminance is not available use 10 mg of pyrantel embonate impurity A RS and 2 mg pyrantel embonate RS (equivalent to about 0.7 mg of pyrantel) per mL dimethylformamide R for solution (4).

Apply separately to the plate 5 μL of each of the solutions (1), (2), (3) and (4).

After application allow the spots to dry for 15 minutes in a current of air. Develop over a path of 12 cm. After removing the plate from the chromatographic chamber allow it to dry in a current of air for 10 minutes. Examine the chromatogram in ultraviolet light (254 nm).

Pyrantel and related substances have the following Rf values: impurity A about 0.2; pyrantel about 0.3; embonic acid about 0.9. The test is not valid unless the chromatogram obtained with solution (4) exhibits three well-separated spots.

In the chromatogram obtained with solution (1) any spot, other than the two principal spots, is not more intense than the pyrantel spot in the chromatogram obtained with solution (2) (1.0%). Disregard any spot remaining at the point of application.

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets and transfer a quantity containing the equivalent of about 25 mg of pyrantel into a 100 mL volumetric flask. Add 7 mL of a mixture composed of 5 volumes of glacial acetic R, 5 volumes of water R and 2 volumes of diethylamine R. Shake and dilute to volume with acetonitrile R, mix and filter. For solution (2) dilute 1.0 mL of the solution (1) to 100.0 mL with mobile phase. For solution (3) expose 10 mL of solution (1) under 2000 lx illumination for 24 hours. In case a suitable device to provide the requested illuminance is not available transfer 10 mg of pyrantel embonate impurity A RS to a 10.0 mL flask, add 8 mL of solution (1) and make up to volume with dimethylformamide R to obtain solution (3).
Inject separately 20 μL each of solution (1), (2) and (3) and record the chromatograms for 4 times the retention time of pyrantel.

In the chromatogram obtained with solution (3) the following peaks are eluted at the following relative retention with reference to pyrantel (retention time about 14 minutes): embonic acid about 0.5; impurity A about 1.3. The test is not valid unless the resolution factor between the pyrantel peak and the impurity A peak is at least 4.0.

In the chromatogram obtained with solution (1) the area of any impurity peak is not greater than the area of the pyrantel peak obtained with solution (2) (1.0%).

**Assay**

Carry out the operations in subdued light and without any prolonged interruptions, preferably using low-actinic glassware.

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with high-purity base particles of silica gel for chromatography R (5 μm).\(^1\)

As the mobile phase use a mixture of 92.8 volumes of acetonitrile R and 7.2 volumes of a solvent mixture composed of 5 volumes of glacial acetic R, 5 volumes of water R and 2 volumes of diethylamine R.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the chewable tablets containing the equivalent of about 7.0 mg of pyrantel, accurately weighed, into a 50 mL volumetric flask. Add about 30 mL of mobile phase, shake for 10 minutes and dilute with mobile phase to volume, mix and filter. Transfer 2.0 mL of the clear filtrate to a 10 mL volumetric flask, dilute with mobile phase to volume and mix. For solution (2) prepare a solution of 0.40 mg of pyrantel embonate RS (equivalent to about 0.14 mg of pyrantel) per mL mobile phase. Transfer 2.0 mL of this solution to a 10 mL volumetric flask, dilute with mobile phase to volume and mix to obtain a standard preparation having a known concentration of 80 μg of pyrantel embonate RS (equivalent to about 28 μg of pyrantel) per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 288 nm.

Inject separately 20 μL each of solution (1) and (2) and record the chromatograms.

In the chromatogram obtained with solution (2) the peak due to embonic acid is eluted at a relative retention time of about 0.5 with reference to pyrantel (retention time about 14 minutes).

Measure the areas of the peak responses due to pyrantel obtained in the chromatograms from solution (1) and solution (2), and calculate the content of pyrantel (C\(_{11}\)H\(_{14}\)N\(_2\)S) in the chewable tablets, using the declared content of C\(_{11}\)H\(_{14}\)N\(_2\)S,C\(_{23}\)H\(_{16}\)O\(_6\) in pyrantel embonate RS. Each mg of pyrantel embonate C\(_{11}\)H\(_{14}\)N\(_2\)S,C\(_{23}\)H\(_{16}\)O\(_6\) is equivalent to 0.3469 mg of pyrantel C\(_{11}\)H\(_{14}\)N\(_2\)S.

**Impurities**

A. 1-methyl-2-[(1E)-2-(thiophen-2-yl)ethenyl]-1,4,5,6-tetrahydropyrimidine.

\(^{***}\)

\(^{1}\) Shim-pack HRS-SIL column (25 cm × 4.6 mm, 5 μm) has been found suitable.
Dexamethasoni natrii phosphas
Dexamethasone sodium phosphate

This is a draft proposal for The International Pharmacopoeia (Working document QAS/14.579, June 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

[Note from the Secretariat. It is proposed to revise the monograph on Dexamethasone sodium phosphate in The International Pharmacopoeia.]

[Note from the editor. In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and delete in the working document available at the above-mentioned web address.]

\[
\text{C}_{22}\text{H}_{28}\text{FNa}_{2}\text{O}_{8}\text{P}
\]

Relative molecular mass. 516.4


Description. A white or almost white, crystalline powder.

Solubility. Freely soluble in water; slightly soluble in ethanol (~750 g/L) TS; practically insoluble in ether R and methylene chloride R.

Category. Adrenal hormone.

Storage. Dexamethasone sodium phosphate should be kept in a tightly closed container, protected from light.

Additional information. Dexamethasone sodium phosphate is very hygroscopic. Even in the absence of light it is gradually degraded on exposure to a humid atmosphere, the decomposition being faster at higher temperatures. Dexamethasone sodium phosphate may exhibit polymorphism.
Requirements

Definition. Dexamethasone sodium phosphate contains not less than 97.0% and not more than 102% of \(\text{C}_{22}\text{H}_{28}\text{FNa}_{2}\text{O}_{8}\text{P}\), calculated with reference to the anhydrous and ethanol-free substance.

Identity tests

A. Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using silica gel R1 as the coating substance and a freshly prepared mixture of 3 volumes of 1-butanol R, 1 volume of acetic anhydride R and 1 volume of water as the mobile phase. Apply separately to the plate 5 \(\mu\)L of each of 4 solutions in methanol R containing (A) 1 mg of the test substance per ml, (B) 1 mg of dexamethasone sodium phosphate RS per ml, (C) a mixture of equal volumes of solutions (A) and (B), and (D) equal volumes of solution (A) and a solution of 1 mg of prednisolone sodium phosphate RS per ml of methanol R. After removing the plate from the chromatographic chamber allow it to dry in air until the solvents have evaporated, spray it with sulfuric acid/ethanol (20%) TS, heat it at 120°C for 10 minutes, allow it to cool and examine the chromatogram in ultraviolet light (365 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B). The principal spot obtained with solution (C) appears as a single compact spot whereas the chromatogram of solution (D) shows 2 closely running spots.

B. Dissolve 10.0 mg of the test substance in 5 ml of water R and dilute to 100.9 ml with dehydrated ethanol R. Transfer 2.0 ml of this solution to a glass-stoppered tube, add 10.0 ml of phenylhydrazine/sulfuric acid TS, mix and heat in a water-bath at 60°C for 20 minutes. Cool immediately. The absorbance (1.6) measured at the absorption maximum at about 419 nm is at least 0.20.

C. Heat carefully 0.04 g of the test substance with 2 ml of sulfuric acid (~1760 g/L) TS until white fumes are evolved, add drop by drop nitric acid (~1000 g/L) TS until oxidation is complete and cool. Add 2 ml of water, heat until white fumes are again evolved, cool, add 10 ml of water and neutralize with ammonia (~100 g/L) TS using pH-indicator paper R. Keep half of the solution for test D. The remaining solution yields reaction A described under 2.1 General identification tests as characteristic of orthophosphates.

D. The solution prepared in test C yields reaction B described under 2.1 General identification tests as characteristic of sodium.

Specific optical rotation. Use a 10 mg/mL solution of the test substance in water R and calculate with reference to the anhydrous and ethanol-free substance; \([\alpha]_{D}^{20^\circ}\) = +75 to +83.

Clarity of solution. A solution of 0.10 g of the test substance in 10 ml of carbon-dioxide-free water R is clear.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using about 0.3 g of the substance. The sum of the contents of water and ethanol (described below), both calculated in mg/g, is not more than 130 mg/g.

Ethanol. Carry out the test as described under 1.14.5 Gas chromatography with the apparatus equipped with an injection system for the performance of static head-space chromatography. 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 \(\mu\)m).
As a 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.

The following head-space injection conditions may be used:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equilibration temperature (°C)</td>
<td>80</td>
</tr>
<tr>
<td>Equilibration time (min)</td>
<td>60</td>
</tr>
<tr>
<td>Transfer line temperature (°C)</td>
<td>85</td>
</tr>
<tr>
<td>Pressurization time (s)</td>
<td>30</td>
</tr>
<tr>
<td>Injection volume (ml)</td>
<td>1</td>
</tr>
</tbody>
</table>

Maintain the temperature of the column at 30°C for 7 minutes then raise the temperature at a rate of 35°C per minute to 180°C and maintain for 10 minutes, 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 the test substance in water R and dilute to 20.0 ml with the same solvent. Introduce 5.0 ml of this solution and 1.0 ml of water R into a headspace vial. Prepare two more vials.

Reference solutions. Add 0.100 g of ethanol R to water R and dilute to 200.0 ml with the same solvent. Transfer respectively 2.0 ml, 4.0 ml and 6.0 ml in separate headspace injection vials and bring the volume to 6.0 ml with water R if necessary.

Blank solution. Introduce 6.0 ml of water R into a headspace vial.

Analyse the blank solution and then alternatively three times the test solution and the three reference solutions.

The test is not valid unless the relative standard deviation on the areas of the peaks obtained from the test solutions is not more than 5%.

Calculate the ethanol content by using the results obtained with the test solution and with the reference solutions; the ethanol content is not more than 30 mg/g.

**pH value**\(^{(1,13)}\). pH of a 10 mg/mL solution in carbon-dioxide-free water R, 7.5–9.5.

**Related substances**

Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (12.5 cm × 4.6 mm) packed with base-deactivated particles of silica gel the surface of which has been modified with chemically-bonded octylsilyl gel groups (5 µm) and end-capped.

Prepare solution (A) by dissolving 7.0 g of ammonium acetate R in 1000 ml of water R.

The mobile phase for the gradient elution consists of a mixture of mobile phase A and mobile phase B using the following conditions:

- **Mobile phase A:** Mix 30 volumes of solution (A) with 35 volumes of water R, adjust to pH 3.8 then add 35 volumes of methanol R.
- **Mobile phase B:** 30 volumes of solution (A) adjusted to pH 4.0 with glacial acetic acid R and 70 volumes of methanol R.
Operate with a flow of 1.0 ml/min. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm. Maintain the column temperature at 30°C.

Prepare the following solutions in mobile phase A. For solution (1) use 1.0 mg of the test substance per ml. For solution (2) use a solution containing 20 µg of betamethasone sodium phosphate RS per ml and 20 µg of dexamethasone sodium phosphate RS per ml. For solution (3) mix equal volumes of solution (2) and a solution containing 20 µg of dexamethasone RS per ml. For solution (4) dilute a suitable volume of solution (1) to obtain a concentration of 10 µg of dexamethasone sodium phosphate per ml.

Inject 20 µL of solution (2). The test is not valid unless the resolution between the peaks due to dexamethasone phosphate (retention time about 22 min) and betamethasone phosphate (with a relative retention time of about 0.95) is at least 2.0.

Inject alternatively 20 µL each of solutions (1), (3) and (4). In the chromatogram obtained with solution (3) the following peaks are eluted at the following relative retention with reference to dexamethasone phosphate (retention time about 22 min): impurity B (betamethasone phosphate): about 0.95; impurity A (dexamethasone): about 1.37. The chromatogram obtained with solution (1) may show the following impurities at the following relative retention with reference to dexamethasone phosphate: impurity C: about 0.5; impurity D: about 0.6; impurity E: about 0.8; impurity F: about 0.92; impurity B: about 0.95; impurity H: about 1.19; impurity A: about 1.37; impurity G: about 1.41.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 0.75, is not greater than 0.5 times the area of the principal peak obtained with solution (4) (0.5%);  
- the area of any peak corresponding to impurity G is not greater than 0.3 times the area of the principal peak obtained with solution (4) (0.3%);  
- the area of any peak corresponding to each impurity B, C, D, E or F is not greater than 0.2 the area of the principal peak obtained with solution (4) (0.2%);  
- the area of any other peak, other than the principle peak, is not greater than 0.1 the area of the principal peak obtained with solution (4) (0.1%);  
- the sum of the corrected area of any peak corresponding to impurity A and the areas of all other peaks, other than the principal peak, is not greater than the area of the principal peak obtained with the solution (4) (1.0%).

Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (4) (0.05%).
Assay
Dissolve about 0.2 g, accurately weighed, in sufficient water to produce 200 ml. Dilute 5 ml to 250 ml with water and measure the absorbance of this solution \((1.6)\) in a 1 cm layer at the maximum at about 241 nm. Calculate the content of \(\text{C}_{22}\text{H}_{28}\text{FNa}_{2}\text{O}_{8}\text{P}\), using the absorptivity value of 29.7 \(\left(\varepsilon_{1 cm} = 297\right)\).

Additional requirements for Dexamethasone sodium phosphate for parenteral use
Complies with the monograph for Parenteral preparations.

Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 31.3 IU of endotoxin per mg.

Impurities

A. 9-fluoro-11\(\beta\),17,21-trihydroxy-16\(\alpha\)-methylpregna-1,4-diene-3,20-dione (dexamethasone),

B. 9-fluoro-11\(\beta\),17-dihydroxy-16\(\beta\)-methyl-3,20-dioxopregna-1,4-dien-21-yl dihydrogen phosphate (betamethasone phosphate),

C, D, E, F. for each impurity, one or more diastereoisomer(s) of (9-fluoro-11\(\beta\),17a-dihydroxy-16-methyl-3,17-dioxo-D-homo-androsta-1,4-dien-17a-yl)methyl dihydrogen phosphate (undefined stereochemistry at C-16 and C-17a), or
(9-fluoro-11β,17-dihydroxy-16α-methyl-3,17a-dioxo-D-homo-androsta-1,4-dien-17-yl)methyl dihydrogen phosphate (undefined stereochemistry at C-17),

G. 9-fluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid,


ICRS referred to:
betamethasone sodium phosphate RS  (already established as an ICRS)
dexamethasone RS  (already established as an ICRS)
dexamethasone sodium phosphate RS  (already established as an ICRS)
prednisolone sodium phosphate RS  (already established as an ICRS)

Test solutions to be added
Sulfuric acid/ethanol (10%) TS
Cool separately 20 ml of sulfuric acid (~1760 g/L) TS and 60 ml of ethanol (~750 g/L) TS to about -5°C. Carefully add the acid to the ethanol, keeping the solution as cool as possible, mix gently and dilute to 100 ml with ethanol.

Note: Sulfuric acid/ethanol (20%) TS must be freshly prepared.

***
Dexamethasoni phosphatis injectio
Dexamethasone phosphate injection

This is a draft proposal for The International Pharmacopoeia (Working document QAS/14.580, June 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

[Note from the Secretariat. To prevent oxidative decomposition of dexamethasone phosphate in aqueous solution sodium metabisulfite is used as an antioxidant. Dijkstra and Dekker1 reported the addition of bisulfite at the C-1 of the corticosteroid. Comments are in particular sought regarding an appropriate limit for this adduct (impurity I) (see also test for related substances).]

Description. A clear, colourless solution

Category. Adrenal hormone.

Storage. Dexamethasone phosphate injection should be kept in a tightly closed container, protected from light. It should not be allowed to freeze.

Labelling. The designation on the container should state the amount of active ingredient as the equivalent quantity of Dexamethasone phosphate in a suitable dose volume.

Additional information. Strength in the current WHO Model list of essential medicines for dexamethasone: 4 mg/mL (as disodium phosphate salt) in 1 ml ampoule. Strength in the current WHO Model list of essential medicines for children: 4 mg/mL (as disodium phosphate salt) in 1 ml ampoule.

4 mg of dexamethasone phosphate is approximately equivalent to 4.37 mg of dexamethasone sodium phosphate.

Requirements
Complies with the monograph for Parenteral Preparations.

Definition. Dexamethasone sodium phosphate injection is a sterile solution of Dexamethasone sodium phosphate in water for injections. It contains not less than 90.0% and not more than 110.0% of the amount of Dexamethasone phosphate C_{22}H_{30}FO_8P stated on the label.

Identity tests
A. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R2 as the coating substance and a mixture of 60 volumes of 1-butanol R, 20 volumes of acetic acid (~300 g/L) TS and 20 volumes of water R. Apply separately to the plate 5 µL of the following 3 solutions in methanol R. For solution (A) dilute a volume of the injection

---

to obtain a solution containing 1.0 mg of dexamethasone phosphate per ml. For solution (B) use dexamethasone sodium phosphate RS to obtain a solution containing 1.0 mg of dexamethasone phosphate per ml. For solution (C) use dexamethasone sodium phosphate RS and prednisolone sodium phosphate RS to obtain a solution containing 1.0 mg of dexamethasone phosphate and 1.0 mg of prednisolone phosphate per ml. After removing the plate from the chromatographic chamber allow it to dry in air and heat at 110°C for 10 minutes. Spray the hot plate with sulfuric acid/ethanol (20%) TS and heat the plate at 120°C for 10 minutes, allow it to cool and examine the chromatogram in daylight and in ultraviolet light (365 nm).

The test is not valid unless the chromatogram obtained with solution (C) shows 2 spots which may, however, not be completely separated.

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

B. See the test described under “Assay”. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

**pH value (1.13).** pH of the injection, 7.0–8.5.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography using the chromatographic conditions given under “Assay”.

Prepare the following solutions in mobile phase A. For solution (1) dilute a volume of the injection to obtain a concentration equivalent to 1 mg of dexamethasone sodium phosphate per ml. For solution (2) use a solution containing 20 µg of betamethasone sodium phosphate RS per ml and 20 µg of dexamethasone sodium phosphate RS per ml. For solution (3) mix equal volumes of solution (2) and a solution containing 20 µg of dexamethasone RS per ml. For solution (4) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 10 µg of dexamethasone sodium phosphate per ml.

Inject 20 µL of solution (2). The test is not valid unless the resolution between the peaks due to dexamethasone phosphate (retention time about 22 min) and betamethasone sodium phosphate (with a relative retention time of about 0.95) is not less than 2.0.

Inject alternatively 20 µL each of solutions (1), (3) and (4). In the chromatogram obtained with solution (3) the following peaks are eluted at the following relative retention with reference to dexamethasone phosphate (retention time about 22 min): impurity B (betamethasone phosphate): about 0.95; impurity A (dexamethasone): about 1.37. The chromatogram obtained with solution (1) may show the following impurities at the following relative retention with reference to dexamethasone phosphate: impurity I: about 0.13; impurity C: about 0.5; impurity D: about 0.6; impurity E: about 0.8; impurity F: about 0.92; impurity B: about 0.95; impurity H: about 1.19; impurity A: about 1.37; impurity G: about 1.41.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 0.75, is not greater than 0.5 times the area of the principal peak obtained with solution (4) (0.5%);
- the area of any peak corresponding to impurity I is not greater than X [to be determined] times the area of the principal peak obtained with solution (4) (X %) [to be determined].
[Note from the Secretariat. To prevent oxidative decomposition of dexamethasone phosphate in aqueous solution sodium metabisulfite is used as an antioxidant. Dijkstra and Dekker\(^{1}\) reported the addition of bisulfite at the C-1 of the corticosteroid. Comments are in particular sought regarding an appropriate limit for this adduct (impurity I).]

Assay

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (12.5 cm × 4.6 mm) packed with base-deactivated particles of silica gel the surface of which has been modified with chemically-bonded octylsilyl gel groups (5 µm) and end-capped.

Prepare solution (A) by dissolving 7.0 g of ammonium acetate R in 1000 ml of water R.

The mobile phase for the gradient elution consists of a mixture of mobile phase A and mobile phase B using the following conditions:

Mobile phase A: Mix 30 volumes of solution (A) with 35 volumes of water R, adjust to pH 3.8 then add 35 volumes of methanol R.

Mobile phase B: 30 volumes of solution (A) adjusted to pH 4.0 with glacial acetic acid R and 70 volumes of methanol R.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (%v/v)</th>
<th>Mobile phase B (%v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3.5</td>
<td>90</td>
<td>10</td>
<td>Isocratic</td>
</tr>
<tr>
<td>3.5–23.5</td>
<td>90–60</td>
<td>10–40</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>23.5–34.5</td>
<td>60–5</td>
<td>40–95</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>34.5–50</td>
<td>5</td>
<td>95</td>
<td>Isocratic</td>
</tr>
<tr>
<td>50–55</td>
<td>5–90</td>
<td>95–10</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>55–65</td>
<td>90</td>
<td>10</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate with a flow of 1.0 ml/min. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm. Maintain the column temperature at 30°C.

Prepare the following solutions in mobile phase A. For solution (1) dilute a volume of the injection to obtain a concentration equivalent to 80 µg dexamethasone phosphate per ml (approximately equivalent to 87 µg dexamethasone sodium phosphate). For solution (2) use a solution containing 87 µg of dexamethasone sodium phosphate RS per ml. For solution (3) use a solution containing 20 µg of betamethasone sodium phosphate RS per ml and 20 µg of dexamethasone sodium phosphate RS per ml.

Inject 20 µL of solution (3). The test is not valid unless the resolution between the peaks due to dexamethasone phosphate (retention time about 22 min) and betamethasone phosphate (with a relative retention time of about 0.95) is at least 2.0.

Inject alternatively 20 µL each of solutions (1) and (2). Measure the areas of the peak responses corresponding to dexamethasone phosphate and calculate the content of dexamethasone phosphate, \(\text{C}_{22}\text{H}_{30}\text{FO}_8\text{P}\), in the injection using the declared content of \(\text{C}_{22}\text{H}_{30}\text{FO}_8\text{P}\) in dexamethasone sodium phosphate RS.

**Bacterial endotoxins.** Carry out the test as described under 3.4 Test for bacterial endotoxins; contains less than 34.2 IU of endotoxin per mg dexamethasone phosphate.
Impurities
The impurities limited by the requirements of this monograph include those listed in the monograph for Dexamethasone sodium phosphate and the following:

I. Dexamethasone bisulfite adduct [chemical name and formula to be added]

ICRS referred to:

betamethasone sodium phosphate RS
(already established as an ICRS)

dexamethasone RS
(already established as an ICRS)

dexamethasone sodium phosphate RS
(already established as an ICRS)

prednisolone sodium phosphate RS
(already established as an ICRS)

Test solutions to be added

Sulfuric acid/ethanol (20%) TS

Cool separately 20 ml of sulfuric acid (~1760 g/L) TS and 60 ml of ethanol (~750 g/L) TS to about -5°C. Carefully add the acid to the ethanol keeping the solution as cool as possible, mix gently and dilute to 100 ml with ethanol.

Note: Sulfuric acid/ethanol (20%) TS must be freshly prepared.

***
Atazanaviri sulfas
Atazanavir sulfate

This is a revised draft proposal for The International Pharmacopoeia (Working document QAS/13.566/Rev.1, June 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidtth@who.int.

Molecular formula. C_{38}H_{52}N_{6}O_{7}·H_{2}O·S

Relative molecular mass. 802.9

Chemical name.
Dimethyl (3S,8S,9S,12S)-9-benzyl-3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-6-[(4-(pyridin-2-yl)phenyl)methyl]-2,5,6,10,13-pentaazatetradecanedioate monosulfate (3S,8S,9S,12S)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[(4-(2-pyridinyl)phenyl)methyl]-2,5,6,10,13-pentaazatetradecanedioic acid 1,14-dimethyl ester, sulfate (1:1); CAS 229975-97-7

Description. A white to a pale yellow crystalline powder.

Solubility. Freely soluble in methanol, practically insoluble in water.

Category. Antiretroviral (protease inhibitor).

Storage. Atazanavir sulfate should be kept in a tightly closed container.

Additional information. Atazanavir sulfate is slightly hygroscopic and may exhibit polymorphism.

Requirements
Atazanavir sulfate contains not less than 99.0% and not more than 101.0% of C_{38}H_{52}N_{6}O_{7}·H_{2}SO_{4} calculated on the dried basis.

[Note from the Secretariat. Comments are being sought in particular on the suitability of the proposed content limits.]

Identity tests
Either test A and D, or test B, C and D should be performed.
A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from atazanavir sulfate RS or with the reference spectrum of atazanavir sulfate. If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the test substance and atazanavir sulfate RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from atazanavir sulfate RS.

B. Carry out test B.1, or where UV detection is not available, test B.2.

B.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 9.5 volumes of dichloromethane R and 0.5 volumes of 2-propanol R as the mobile phase. Apply separately to the plate 10 μl of each of 2 solutions in methanol R containing (A) 1 mg of the test substance per mL and (B) 1 mg of atazanavir sulfate RS per mL. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air or in a current of air. Examine the chromatogram in ultraviolet light (254 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described under test B.1, but using a plate containing silica gel R5 as the coating substance. Spray the plate with potassium permanganate, basic (~5 g/L) TS. Examine the chromatogram in daylight. The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).

C. The absorption spectrum of a 10 μg/mL solution in methanol R, when observed between 230 nm and 340 nm, exhibits two maxima at about 250 nm and 280 nm.

D. A 20 mg/mL solution yields Reaction A described under 2.1 General identification tests as characteristic of sulfates.

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to method A; not more than 20 μg/g.

Sulfated ash (2.3). Not more than 1.0 mg/g.

Loss on drying. Dry for 3 hours at 105 °C; it loses not more than 10.0 mg/g.

Specific optical rotation. Use a 10 mg/mL solution in equal volumes of methanol R and water R at 22°C calculated with reference to the anhydrous substance; the optical rotation is between -40° and -44°.

Related substances

Carry out the test as described under 1.14.4 High–performance liquid chromatography using a column (150 mm x 4.6 mm) packed with end-capped, base-deactivated particles of silica gel the surface of which has been modified with chemically-bonded octylsilyl groups (5 μm). Use the following conditions for gradient elution:

Mobile phase A: 0.02 M phosphate buffer pH 3.5, acetonitrile R (70:30 v/v).

Mobile phase B: 0.02 M phosphate buffer pH 3.5, acetonitrile R. (30:70 v/v)

An Inertsil C8 column has been found suitable.
Prepare the phosphate buffer pH 3.5 by dissolving 2.72 g of anhydrous potassium dihydrogen phosphate R in 800 mL of water R, adjust the pH to 3.5 by adding phosphoric acid (~105 g/L) TS and dilute to 1000 mL with water R.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>100</td>
<td>0</td>
<td>Isocratic</td>
</tr>
<tr>
<td>2–10</td>
<td>100–75</td>
<td>0–25</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>10–30</td>
<td>75–50</td>
<td>25–50</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>30–45</td>
<td>50–0</td>
<td>50–100</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>45–50</td>
<td>0</td>
<td>100</td>
<td>Isocratic</td>
</tr>
<tr>
<td>50–52</td>
<td>0–100</td>
<td>100–0</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>52–60</td>
<td>100</td>
<td>0</td>
<td>Isocratic</td>
</tr>
</tbody>
</table>

Prepare the following solutions using as diluent a mixture of equal volumes of water R and acetonitrile R. For solution (1) use 1 mg of the test substance per mL. For solution (2) dilute a suitable volume of solution (1) with the diluent to obtain a concentration equivalent to 5 μg of Atazanavir sulfate per mL. For solution (3) mix 1 mL of solution (1) with 4.5 mL of water R and 0.5 mL of sodium hydroxide (10 g/L) TS and heat the mixture in a water-bath at 85°C for 15 minutes.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 250 nm. Maintain the column at a temperature of 30°C.

Inject 20 μL of solution (3). The test is not valid unless the resolution between the peak due to atazanavir (retention time about 22 minutes) and the peak with a relative retention of about 1.2 is at least 4.

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

In the chromatograms obtained with test solution (1) the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%). The sum of the areas of all peaks, other than the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

**Assay**

Dissolve 0.300 g, accurately weighed, in 30 mL of methanol R and by sonication for 10 minutes. Then add 30 mL of water and titrate with sodium hydroxide (0.1 mol/L) VS, determining the end-point potentiometrically. Each mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 40.145 mg of C_{38}H_{52}N_{6}O_{7}•H_{2}SO_{4}.

***
Atazanavir capsules

This is a revised draft proposal for The International Pharmacopoeia (Working document QAS/13.567/Rev.1, June 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidt@who.int.

Category. Antiretroviral (Protease Inhibitor).

Storage. Atazanavir capsules should be kept in a tightly closed container.

Additional information. Strength in the current WHO Model list of essential medicines: 100 mg, 150 mg, 300 mg of atazanavir (as sulfate). Strength in the current WHO Model List of essential medicines for children: 100 mg, 150 mg, 300 mg of atazanavir (as sulfate).

Each mg of atazanavir (C_{38}H_{52}N_{6}O_{7}) is equivalent to 1.139 mg of atazanavir sulfate (C_{38}H_{52}N_{6}O_{7}•H_{2}SO_{4}).

Requirements

Comply with the monograph for Capsules.

Definition

Atazanavir capsules contain atazanavir sulfate. They contain not less than 90.0% and not more than 110.0% of the amount of atazanavir, C_{38}H_{52}N_{6}O_{7}, stated on the label.

Identity tests

A. Carry out test A.1, or where UV detection is not available, test A.2.

A.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 9.5 volumes of dichloromethane R and 0.5 volumes of 2-propanol R as the mobile phase. Apply separately to the plate 10 µL of each of the following 2 solutions in methanol R. For solution (A) disperse a quantity of the contents of the capsules containing about 20 mg of atazanavir in 10 mL of methanol R, sonicate for 10 minutes, allow to cool to room temperature, dilute to 20 mL, filter and use the filtrate. For solution (B) use 1.1 mg of atazanavir sulfate RS per mL.

After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or a current of air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance, and intensity to that obtained with solution (B).

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using a plate containing silica gel R5 as the coating substance. Spray with potassium permanganate, basic (~5 g/L) TS. Examine the chromatogram in daylight.
The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

B. Disperse a quantity of the contents of the capsules containing about 20 mg of atazanavir in 10 mL of methanol R, sonicate for 10 min, allow to cool to room temperature, dilute to 20 mL and filter. Dilute 1 mL of the filtrate to 100 mL with methanol R. The absorption spectrum (1.6) of the resulting solution, when observed between 230 and 340 nm, exhibits two maxima at about 250 nm and 280 nm.

C. To a quantity of the contents of the capsules equivalent to 0.2 g of atazanavir add 10 mL of a mixture of 1 volume of water R and 1 volume of acetonitrile R, shake and filter. The filtrate yields Reaction A described under 2.1 General identification tests as characteristic of sulfates.

Dissolution

Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 900 mL of dissolution buffer pH 2.5 TS, and rotating the paddle at 50 revolutions per minute. At 45 minutes withdraw a sample of 10 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature. Measure the absorbance (1.6) of a 1 cm layer of the resulting solution, suitably diluted if necessary, at the maximum at about 250 nm. Determine the content of atazanavir (C38H52N6O7) in the medium from the absorbance obtained using an absorptivity value of 15.9 (A1%1cm = 159)1. The amount in solution for each capsule is not less than 75% (Q) of the amount stated on the label.

Related substances

Carry out the test as described under 1.14.4 High–performance liquid chromatography, using a stainless steel column (150 mm x 4.6 mm) packed with end-capped base deactivated particles of silica gel the surface of which has been modified with chemically bonded octylsilyl groups (5 μm).2 Use the following conditions for gradient elution:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>100</td>
<td>0</td>
<td>Isocratic</td>
</tr>
<tr>
<td>2–10</td>
<td>100–75</td>
<td>0–25</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>10–30</td>
<td>75–50</td>
<td>25–50</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>30–45</td>
<td>50–0</td>
<td>50–100</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>45–50</td>
<td>0</td>
<td>100</td>
<td>Isocratic</td>
</tr>
<tr>
<td>50–52</td>
<td>0–100</td>
<td>100–0</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>52–60</td>
<td>100</td>
<td>0</td>
<td>Isocratic</td>
</tr>
</tbody>
</table>

Prepare the phosphate buffer pH 3.5 by dissolving 2.72 g of anhydrous potassium dihydrogen phosphate R in 800 mL of water R, adjust the pH to 3.5 by adding phosphoric acid (~105 g/L) and dilute to 1000 mL with water R.

Prepare the following solutions using as diluent a mixture of equal volumes of acetonitrile R and water R. For solution (1) weigh and mix the contents of 20 capsules. Transfer a quantity of the mixed contents equivalent to 20 mg of atazanavir into a 20 mL volumetric flask. Add about 10 mL of the diluent, sonicate for 10 minutes, allow to cool to room temperature, make up to volume and filter. For solution (2) dilute a suitable volume of solution (1) with the diluent to obtain a concentration of 10 μg of atazanavir per mL. For solution (3) mix 1 mL of solution (1)...

1 Value subject to confirmation.
2 An Inertsil C8 column has been found suitable.
with 4.5 mL of water R and 0.5 mL of sodium hydroxide (10 g/L) TS and heat the mixture in a water bath at 85°C for 15 min. Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 250 nm. Maintain the column at a temperature of 30°C. Inject 20 µL of solution (3). The test is not valid unless the resolution between the peak due to atazanavir (retention time about 22 minutes) and the peak with a relative retention of about 1.2 is at least 4.

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

In the chromatograms obtained with test solution (1) the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%). The sum of the areas of all peaks, other than the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with reference solution (2) (2.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Assay

Either test A or test B may be applied.

A. Carry out the test as described under 1.14.4 High–performance liquid chromatography, using a stainless steel column (150 mm x 4.6 mm) packed with end-capped base deactivated particles of silica gel the surface of which has been modified with chemically bonded octylsilyl groups (5 μm).³

As the mobile phase, use a solution prepared as follows: 60 volumes of acetonitrile R and 40 volumes of 0.02 M phosphate buffer pH 3.5. Prepare the phosphate buffer pH 3.5 according to the procedure described in the related substances test.

Prepare the following solutions using as diluent a mixture of equal volumes of acetonitrile R and water R. For solution (1) weigh and mix the contents of 20 capsules. Transfer a quantity equivalent to 20.0 mg of atazanavir, accurately weighed, into a 20 mL volumetric flask. Add about 10 mL of the diluent, sonicate for about 10 minutes, allow to cool to room temperature and make up to volume. Filter a portion of this solution, discarding the first few mL. Dilute 1.0 mL of the filtrate to 10.0 mL with the diluent. For solution (2) use 0.11 mg of atazanavir sulfate RS per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 250 nm. Maintain the column at a temperature of 30°C. Inject alternatively 20 µL each of solutions (1) and (2) and record the chromatograms for 1.5 times the retention time of atazanavir.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of atazanavir, \( \text{C}_{38}\text{H}_{52}\text{N}_6\text{O}_7 \), using the declared content of \( \text{C}_{38}\text{H}_{52}\text{N}_6\text{O}_7 \) in atazanavir sulfate RS.

B. Weigh and mix the contents of 20 capsules. Transfer a quantity equivalent to 20 mg of atazanavir, accurately weighed, to a 20 mL volumetric flask. Add about 10 mL of methanol R, sonicate for about 10 minutes, allow to cool to room temperature and make up to volume. Filter a portion of this solution through a 0.45 µm filter, discarding the first few mL of the filtrate. Dilute 1.0 mL of the filtrate to 10.0 mL with methanol R. Measure the absorbance of this solution in a 1 cm layer at the maximum at about 250 nm against a solvent cell containing methanol R. Calculate the content of \( \text{C}_{38}\text{H}_{52}\text{N}_6\text{O}_7 \), using an absorptivity value of 15.9 (\( \text{A}_{1\text{cm}} = 159 \)).⁴

³ An Inertsil C₈ column has been found suitable.

⁴ Value subject to confirmation.
Albendazoli compressi
Albendazole chewable tablets

This is a revised draft proposal for The International Pharmacopoeia (Working document QAS/14.592, June 2014).

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidt@who.int.

[Note from the Secretariat. It is proposed to revise the monograph with a view to include a dissolution test and acceptance criterion.]

[Note from the editor. In accordance with WHO editorial policy the text reproduced below does not include tracked changes. Changes from the current monograph are indicated by insert and delete in the working document available at the above-mentioned web address.]

Category. Anthelmintic.

Storage. Albendazole chewable tablets should be kept in a tightly closed container.

Labelling. The designation on the container should state that the tablets may be chewed, swallowed whole or crushed and mixed with food or liquid, and the tablets should be crushed before being given to a young child.

Additional information. Strengths in the current WHO Model list of essential medicines: 400 mg. Strengths in the current WHO Model list of essential medicines for children: 400 mg.

Requirements
Comply with the monograph for Tablets.

Definition. Albendazole chewable tablets contain Albendazole in a suitable basis that may contain suitable flavouring agents. They contain not less than 90.0% and not more than 110.0% of the amount of Albendazole (C\textsubscript{12}H\textsubscript{15}N\textsubscript{3}O\textsubscript{2}S) stated on the label.

Identity tests
• Any two of tests A, B and C may be applied

A. Carry out the test as described under 1.14.1 Thin-layer chromatography using the chromatographic conditions given under "Related substances", Test B. Apply separately to the plate 10 μL each of the following solutions in a mixture of 9 volumes of dichloromethane R and 1 volume of glacial acetic acid R. For solution (A) shake a quantity of the powdered tablets containing about 2.5 mg of Albendazole with 25 mL, filter and use the filtrate. For solution (B) use 0.1 mg of albendazole RS per mL. For solution (C) use 0.1 mg of albendazole RS and 0.1 mg of oxibendazole R per mL. After removing the plate from the chromatographic chamber allow the plate to dry in a current of warm air and examine the chromatogram under ultraviolet light (254 nm). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).
B. See the test described below under “Assay”, Method A. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to the retention time of the peak due to albendazole obtained with solution (3).

C. See the test described under “Assay”, Method B. The absorption spectrum (1.6) of the test solution, when observed between 220 and 340 nm, exhibits maxima at about 231 nm and at 308 nm; the absorbance at 308 nm is about 0.59.

**Dissolution.** Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms using 900 mL of hydrochloric acid (0.1 mol/L) VS as the dissolution medium and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 15 mL of the dissolution medium through an in-line filter. Cool the filtered sample to room temperature. Transfer 1.0 mL of the clear filtrate to a 50 mL volumetric flask and dilute to volume with sodium hydroxide (~4 g/L) TS. Measure the absorbance (1.6) of a 1 cm layer of the resulting solution at the maximum at about 308 nm.

For each of the six tablets tested calculate the total amount of Albendazole (C12H15N3O2S) in the medium, using the absorptivity value of 74.2 (A1%1cm = 742). The amount in solution for each tablet is not less than 80% (Q) of the amount declared on the label.

**Related substances**

• Either method A or method B may be applied.

A. Carry out the test as described under 1.14.4 High performance liquid chromatography using the conditions given below under “Assay”, Method A.

Prepare the following solutions.

Solvent mixture: dilute 1 volume of sulfuric acid R with 99 volumes of methanol R.

For solution (1) transfer a quantity of the powdered tablets containing about 25 mg of Albendazole to a 50 mL volumetric flask. Add 5 mL of the solvent mixture and 20 mL of methanol R and shake to dissolve for about 15 minutes. Dilute to volume with methanol R.

For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL with methanol R. For solution (3) dissolve about 20 mg of albendazole RS and about 20 mg of oxibendazole R in 5 mL of solvent mixture and dilute to 100.0 mL with methanol R.

Inject separately 20 µL each of solutions (1), (2) and (3). Record the chromatogram for about 25 minutes.

In the chromatogram obtained with solution (3) the peak due to oxibendazole is eluted at a retention time of about 9.9 min and the peak due to albendazole at a retention time of about 13.6 minutes. The test is not valid unless the resolution factor between the peak due to oxibendazole and the peak due to albendazole is at least 3.0.

In the chromatogram obtained with solution (1):

• the area of any peak, other than the principal peak, is not greater than the area of the peak due to albendazole in the chromatogram obtained with solution (2) (1.0%);

• the area of not more than one such peak is greater than 0.75 times the area of the peak due to albendazole in the chromatogram obtained with solution (2) (0.75%).

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel RS as the coating substance and a mixture of dichloromethane R, glacial acetic acid R and ether R (30:7:3 v/v) as the mobile phase. Apply separately to the plate 10 µL each of the following solutions in a mixture of 9 volumes of dichloromethane R and 1 volume of glacial acetic acid R. For solution (A) shake a quantity of the powdered tablets containing about 250 mg of Albendazole with 25 mL, filter and use the filtrate. For solution (B) use 0.1 mg of albendazole RS per mL. For solution (C) use 0.075 mg of albendazole RS per mL. For
solution (D) use 0.1 mg albendazole RS and 0.1 mg oxibendazole R per mL. After removing
the plate from the chromatographic chamber allow the plate to dry in a current of warm air.
Examine the chromatogram in ultraviolet light (254 nm). The test is not valid unless the
chromatogram obtained with solution (D) shows two clearly separated spots.

In the chromatogram obtained with solution (A) any spot, other than the principal spot, is
not more intense than the principal spot obtained with solution (B) (1.0%) and not more
than one spot is more intense than the principal spot obtained with solution (C) (0.75%).

**Assay**

• Either method A or method B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography
using a stainless steel column (25 cm × 4.6 mm) packed with octadecylsilyl base-
deactivated silica gel for chromatography R (5 µm).

As the mobile phase use a solution prepared as follows: dissolve 1.67 g of monobasic
ammonium phosphate R in 1000 mL of water R, mix and filter. Mix 300 mL of this solution
with 700 mL of methanol R. Make adjustments if necessary.

Prepare the following solutions.

Solvent mixture: dilute 1 volume of sulfuric acid R with 99 volumes of methanol R.

For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets
containing about 100 mg of Albendazole, accurately weighed, to a 50 mL volumetric flask.
Add 5 mL of the solvent mixture and 20 mL of methanol R and shake for about 15 minutes.
Dilute to volume with methanol R, mix and filter, discarding the first 15 mL of the filtrate.
Dilute 5.0 mL of this solution to 50.0 mL with methanol R. For solution (2) transfer 25.0 mg
of Albendazole RS to a 25 mL volumetric flask, add 5 mL of the solvent mixture and 15 mL
of methanol R and shake to dissolve. Dilute to volume with methanol R. For solution (3)
dilute 2.0 mL of solution (2) to 10.0 mL with methanol R. For solution (4) dissolve about 20
mg of oxibendazole R in 5 mL of solvent mixture in a 100 mL volumetric flask, add 20 mL of
solution (2), mix and dilute to volume with methanol R.

Operate with a flow rate of 0.7 mL per minute. As a detector use an ultraviolet
spectrophotometer set at a wavelength of 254 nm.

Inject separately 20 µL each of solutions (1), (3) and (4). The test is not valid unless in the
chromatogram obtained with solution (4) the resolution factor between the peaks due to
albendazole and due to oxibendazole is at least 3.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions
(1) and (3) and calculate the content of Albendazole (C_{12}H_{15}N_{3}O_{2}S) in the tablets using the
declared content of C_{12}H_{15}N_{3}O_{2}S in albendazole RS

B. Weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing
about 20 mg of Albendazole, accurately weighed, to a 50 mL volumetric flask, add 30 mL
of hydrochloric acid/methanol (0.01 mol/L) VS, shake for 15 minutes and dilute to volume
with the same solvent. Mix and filter, discarding the first 10 mL of the filtrate. Transfer 1.0
mL of the subsequent filtrate to a 50 mL volumetric flask and dilute to volume with sodium
hydroxide (~4 g/L) TS. Measure the absorbance of the resulting solution at the maximum
at about 308 nm. Calculate the content of Albendazole (C12H15N3O2S), using the
absorptivity value of 74.2 (A^{1%}_{1cm} = 742).