WHO Drug Information

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Consultation documents

International Nonproprietary Names

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)
MHLW	Ministry of Health, Labour and Welfare, Japan
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

Note:

The online version of this issue (available at www.who.int/medicines/publications/druginformation) has direct clickable hyperlinks to the documents and web pages referenced.

Regulatory collaboration

The International Coalition of Medicines Regulatory Authorities (ICMRA)

A new global collaboration brings together senior leaders to provide coordinated, consistent, and strategic leadership in an increasingly globalized and complex regulatory environment. The International Coalition of Medicines Regulatory Authorities (ICMRA) is a voluntary, executive level entity that provides direction for a range of areas that are common to many regulatory authorities' missions.

The global regulatory environment

Globalization directly affects the protection and promotion of public health everywhere. Medicinal products distributed and used in domestic markets are increasingly global commodities. The manufacturing and distribution supply chains are complex, multi-faceted, globally integrated and may at times be difficult to understand or unravel. The ability of a regulator to assure the safety, quality and efficacy of a medicinal product domestically requires knowledge of and confidence in these supply chains and regulatory oversight at all stages. There is also growing complexity in medicinal products and their ingredients, and managing the risks and benefits requires regulators to consider international collaboration approaches to provide access to regulatory authorities' resources and the best available scientific and technical expertise. The resulting increase of global regulatory networks, usually conducted at the technical/operational level, also calls for increased efficiency in managing the expertise and resources invested in these initiatives. In short, Medicines Regulatory Authorities (MRA) regulate within an extremely complex domain – legally, technically, and scientifically – and recognize that the effectiveness of the plans and approaches used to address these challenges

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depends upon strategic-level leadership and new ways of working around the globe including information-sharing which gives room for potential synergies.

A collective, global understanding of these realities has fueled international discussions over the last few years including at the World Health Assembly, the World Health Organization's International Conference of Drug Regulatory Authorities (ICDRA), and the International Summit of Heads of Medicines Regulatory Agencies. Leaders of MRAs are harnessing this momentum to establish a new way of collaborating, the International Coalition of Medicines Regulatory Authorities (ICMRA).

What is the ICMRA?

The ICMRA is a venue for heads of national regulatory authorities around the world to enable a shared strategic leadership to address current and emerging global regulatory challenges and to better leverage resources in ways that expand global regulatory reach *(1)*.

What sets the ICMRA apart from other existing regulatory initiatives is that it brings together senior leaders to provide strategic, high-level advocacy and leadership. ICMRA can provide direction for a range of areas and activities that are common to many MRAs' missions and goals, identify areas for potential synergies to be made, and wherever possible, leverage existing efforts to maximize global impact. Four over-arching objectives help to guide the ICMRA:

- to protect human health throughout the life-cycle of medicinal products;
- to enable regulatory conditions which facilitate improved access to and availability of safe, efficacious and quality medicinal products. This also includes enabling innovation and advancing regulatory science as it related to medicine research and development;
- to promote coherent and strategic multilateral cooperation among regulatory authorities, in order to strengthen mutual reliance, trust, synergies and regulatory systems, and to achieve better use of collective resources/work products and sharing of best practices; and
- to promote the leveraging of regulatory authorities' resources, including knowledge and expertise.

ICMRA has a medicines focus at this stage, and participants are currently working on selected joint efforts to stimulate collaborative thinking and action, piloting new ways of working to build mutual reliance, and facilitating early and timely identification of emerging public health crises that intersect with medical regulatory authorities *(Box 1)*.

Box 1. **Current ICMRA Working Groups**

1) Governance
2) Mapping
3) Communications/Outreach
4) GMP Inspections
5) Generic Medicines
6) Rapid Sharing of Information
7) Capacity Building

Indeed, much of ICMRA's true potential is in its ability to maintain a consistent and open dialogue among the heads of MRAs, enabling them to quickly connect on issues of mutual priority or concern. A good example of this coordinated response is the September 4, 2014 ICMRA Statement on Ebola *(2)*.

The ICMRA is currently operating in an interim period (2013-2015) as it builds a strong foundation for governance and sustainable collaboration. It is supported by a Secretariat and guided by a Chair, two Vice-Chairs[1], and a Management Committee[2]. Membership[3], currently envisioned by a small number of current members emanating from earlier heads of medicines summits[4], will be voluntary and will include regulatory authorities for medicinal products[5].

Envisioning a framework for action

Over time, ICMRA will enable a global architecture to support enhanced communication, information-sharing and crisis response. ICMRA will also focus on strengthening regulatory systems and capacity, and increasing awareness of and appreciation for the importance of strong regulatory systems and functions within national, sub-regional, and global contexts.

ICMRA benefits are multi-faceted and most importantly enable MRAs to coalesce around regulatory issues of mutual priority within a 21st century environment. ICMRA benefits will be stronger confidence and collaboration among regulators, less duplication of effort and more strategic use of human and financial resources. All heads of national regulatory authorities are encouraged to remain apprised of developments within ICMRA and engage with the ICMRA.

Potential for global synergies

As ICMRA begins to determine where it can best add value within an environment of various global regulatory efforts, it is clear that the potential for synergies are numerous. There are many well-established technical and scientific bodies already serving unique purposes with specific mandates, for example, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the Pharmaceutical Inspection Convention and Pharmaceutical

[1] Health Canada's Health Products and Food Branch (HC-HPFB) is the interim ICMRA Chair and interim Secretariat, with Ireland's Health Product Regulatory Authority and Japan's Ministry of Health, Labour and Welfare and Pharmaceuticals and Medical Devices Agency as Vice-Chairs.

[2] ICMRA Management Committee membership includes: Australia, Brazil, Canada, China, Europe, Ireland, Italy, Japan, the Netherlands, Singapore, South Africa, the United Kingdom, and the United States.

[3] Current membership in the ICMRA includes the Heads of the regulatory authorities of: Australia (TGA), Brazil (ANVISA), Canada (HPFB-HC), China (CFDA), Europe (EMA and EC), France (ANSM), Germany (PEI), Ireland (HPRA), Italy (AIFA), Japan (PMDA and MHLW), Korea (MFDS), Mexico (COFEPRIS), the Netherlands (MEB), New Zealand (Medsafe), Nigeria (NAFDAC), Singapore (HSA), South Africa (MCC), Switzerland (Swissmedic), the United Kingdom (MHRA) and the United States (FDA), with the World Health Organization (WHO) as an observer.

[4] The International Summit of Heads of Medicines Regulatory Agencies is an annual meeting that serves as an important forum for the exchange of information, views and regulatory strategies among the chief executives of major and like-minded medicines regulatory agencies.

[5] Interested authorities should contact the ICMRA interim Chair, Health Canada's Health Products and Food Branch, ICMRA.SEC@HC-SC.GC.CA.

Inspection Co-operation Scheme (PIC/S). Dialogue between ICMRA and these organizations has already begun with the purpose of opening and maintaining ongoing communication on issues of common concern and interest. ICMRA will continue to connect with other initiatives, including those with a regional focus.

ICMRA continues to identify areas of potential synergy on discrete topics including: Good Manufacturing Practices (GMP), information-sharing and information-sharing platforms, Unique Facility Identifiers (UFI), generic drugs, and capacity building. Using ICMRA as a venue to convene MRAs on topics of mutual priority can yield significant benefits.

In sum, the ICMRA is a new governance and leadership model in the global regulatory environment. By providing strategic and high-level oversight and guidance and early thinking, we, as the leaders of our respective regulatory authorities, hope to better leverage our resources, address issues of mutual concern, and increase shared thinking and action. We encourage all WHO Member States to increase their understanding of ICMRA and become engaged as we move to transform the global regulatory landscape.

References

1 International Coalition of Medicines Regulatory Authorities (ICMRA). Fact Sheet. September 2014.

2 Statement on international regulatory cooperation regarding Ebola [News release]. Health Canada, 4 September 2014.

Norms and standards

Good review practices: guidelines for national and regional regulatory authorities *

This is a summary of a guideline on good regulatory review practices developed through an inter-organizational collaboration. It is the first set of guidelines of its kind globally and addresses an important gap identified at the 2012 International Conference of Drug Regulatory Authorities (ICDRA).

The full text as adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2014 will be published as an annex to the Expert Committee's report; the draft published for comment prior to the Committee's meeting is available on the WHO web site *(1)*.

The benefits of good review practices

Regulatory authorities (RAs) are increasingly seeking ways to improve their performance and ensure the quality of their regulatory systems. Medical product review is that part of regulatory work that forms the scientific foundation for regulatory decisions on marketing authorizations. It requires a highly complex, multidisciplinary assessment of product data to ensure that products submitted for regulatory approval meet adequate scientific and evidentiary standards for safety, efficacy and quality.

Implementation of good review practices helps RAs to achieve timely reviews with high quality outcomes, with a significant impact on public health, for example in terms of patients' access to important medical products, and costs to both government and applicants.

Good review practice also facilitates progress towards regulatory convergence through the exchange of review reports and better mutual understanding among RAs. This is a significant benefit as the use of reviews and decisions reached by other RAs is expected to become increasingly important in achieving review efficiencies in the face of pressures on resources.

Guideline development

In June 2013 the Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC) convened an expert working group with WHO representation to develop a draft good review practices document, intended to cover both medicines and medical devices, for submission to WHO in early 2014. WHO risk management principles *(2)* and the results of an APEC survey *(3)* were among the key references used in developing this text.

The draft document was accepted for parallel public consultation processes

* Asia-Pacific Economic Cooperation (APEC) Regulatory Harmonization Steering Committee (RHSC) good review practices (GRevP) with the participation of Working Group Members representing the regulatory authorities (RAs) from the economies of Australia, Canada, Taipei (China), Japan, Republic of Korea, Saudi Arabia, Singapore, United States of America; and representatives of the Centre for Innovation in Regulatory Science (CIRS); and the Food and Drug Administration Alumni Association International (FDAAA).

for both the WHO Expert Committee on Specifications for Pharmaceutical Preparations and the WHO Expert Committee on Biological Standardization. This led to a guidance text on good review practices for regulatory authorities being adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its forty-ninth meeting, held on 13–17 October 2014 in Geneva.

Objective and scope

The objective of the document is to provide high-level guidance on the principles and processes of good review practice for use across a range of RA maturities. It is not intended to provide detailed instruction on how to conduct a scientific review. Rather, it 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. The principles and elements described in this document can be adapted to meet the continuous needs for improvement of a diverse range of RAs.

Although the document was written to provide guidance on pharmaceutical products and biologicals and higher-risk medical devices used in humans, the concepts may be applied to other types of medical products. Similarly, the concepts could also be applied to the entire product life cycle from investigational testing to new product applications, updates or variations to existing marketing authorizations and maintenance of the product.

What is good review practice?

The guidelines define good review practices (GRevPs) as *"documented best practices for any aspect related to the process, format, content and management of a medical product review. The objective of GRevPs is to help achieve timeliness, predictability, consistency, transparency, clarity, efficiency and high quality in both the content and management of reviews. This is done through the development of review tools (for example, standard operating procedures (SOPs) and templates) and reviewer learning activities (for example, training courses, mentoring, orientation packages and discussion sessions). To promote continuous improvement, all aspects of GRevPs should be continuously evaluated and updated."*

The document proposes ten key principles of a good review as a general guide for RAs (see *Box 1*).

Managing the review

The principles of project management and quality management are critical to achieve efficient and effective review processes.

Project management refers to the planning, organizing and resourcing necessary to achieve a complete and high-quality review of an application within a specified time frame. RAs should identify the most suitable techniques enabling them to monitor the progress of one or many applications under review at any one time, to help in decision-making on how to balance workload against resources, and to enable monitoring and/or its interpretation by the relevant people.

Quality management – the coordinated activities that direct and control an organization with regard to quality – ensures that GRevPs are in place, regularly monitored and subject to continuous improvement. The quality cycle is made up of four key components:

- say what you do,
- do what you say,
- prove it, and
- improve it.

Box 1: **Ten key principles of a good review**

Balanced
A good review is objective and unbiased.

Considers context
A good review considers the data and the conclusions of the applicant in the context of the proposed conditions of use and storage, and may include perspectives from patients, health-care professionals and other RAs' analyses and decisions.

Evidence-based
A good review is evidence-based and reflects both the scientific and regulatory state of the art. It integrates legislative, regulatory and policy frameworks with emerging science.

Identifies signals
A good review comprehensively highlights potential areas of concern identified by the applicant and the reviewers.

Investigates and solves problems
A good review provides both the applicant's and the reviewers' in-depth analyses and findings of key scientific data and uses problem-solving, regulatory flexibility, risk-based analyses and synthesis skills to devise and recommend solutions and alternatives where needed.

Makes linkages
A good review provides integrated analysis across all aspects of the application: preclinical, nonclinical, clinical, chemistry/biocompatibility, manufacturing and risk management plan. It includes timely communication and consultation with applicants, internal stakeholders and, as needed, with external stakeholders who have expertise relevant to the various aspects of the application.

Utilizes critical analyses
A good review assesses the scientific integrity, relevance and completeness of the data and proposed labelling, as well as the interpretation thereof, presented in the application.

Thorough
A good review reflects adequate follow-through of all the issues by the reviewers.

Well-documented
A good review provides a well-written and thorough report of the evidence-based findings and conclusions provided by the applicant in the dossier, and the reviewers' assessment of the conclusions and rationale for reaching a decision. It contains clear, succinct recommendations that can stand up to scrutiny by all the parties involved and could be leveraged by others.

Well-managed
A good review applies project and quality management processes, including clearly defined steps with specific activities and targets.

This cycle ensures that GRevPs are not merely theoretical guidelines ("say what you do") but become embedded in the daily practice of an agency ("do what you say"). Quality management can also help an agency review its practice ("prove it") and evolve where necessary, either in response to evolving regulatory science or through the adoption of new review processes and procedures ("improve it").

Standard operating procedures (SOPs) enable RAs to outline workflow processes, handle and review product applications in a consistent manner, and facilitate staff training. SOPs can be complemented by companion documents such as guidelines, templates and checklists, and can be designed both for internal use and to guide applicants seeking marketing authorization.

SOPs will require updating in line with evolving scientific progress, international harmonization of guidelines, changes in review strategy, available resources, increased volume of applications, collaborative work-sharing, and national laws and regulations, among others.

Review process stages

The review process has two key stages: firstly a validation stage (also called screening) to identify missing information in the application, ensuring that time and review resources are only spent on applications that have enough data to allow critical analysis, signal identification and regulatory decision-making, and secondly the actual scientific review, discussed in more detail below. Applicants should be made clearly aware of the RA's expectations at both stages.

Communications

Good communication is critical and has many advantages for RAs, applicants and the public. It can improve the efficiency of the development and review processes and thus ultimately speed up patient access to good quality medical products.

Communications can take many active forms, from providing information on RAs' websites to engaging with the international community on RA projects. The guidelines outline best practices for communication and their benefits at various levels:

- within RAs, for effective coordination of organizational units carrying out different pre- and postmarketing functions (for example pharmacovigilance, inspection and others);
- between RAs, enabling peer collaboration and cooperation, whereby interagency communications can also facilitate greater regulatory convergence;
- with applicants, to provide insight into the RA's current thinking and expectations, enabling a mutual better understanding and therefore better quality applications;
- with external experts (for example from academic institutions, industry associations, patient organizations and medical or scientific organizations) to make use of valuable expertise while ensuring confidentiality and absence of conflict of interest; and
- with the public, to foster awareness, understanding of and confidence in the RA, and to obtain input on proposed regulations and/or specific applications.

Review personnel

The quality, timeliness and success of medical product reviews are dependent on a sufficient number of competent reviewers. The guideline outlines the expertise, competencies and training required to deal with the various aspects of managing and conducting reviews.

Reviewers may be RA staff, external experts or both. Reviewers should be free of actual or perceived conflicts of interests, meaning that the review decision or recommendation is not likely to be influenced by personal, family, financial or professional motives, including those of employers when an external expert is also a consultant to the regulated industry. Review staff should follow sound ethical practices.

Reviewers should keep their scientific expertise up to date. The guidelines propose various approaches for professional development of review staff, making use of opportunities both within and outside the RA.

Critical thinking and good judgement

Critical thinking is important for reviewers to make decisions that are reproducible and clearly understood by others. Reviewers should have the ability to critically appraise the information presented in an application and not just accept it as presented. This skill can be strengthened by learning from

senior reviewers and through discussion among reviewers and external experts on application-specific issues.

Good judgement is required for reviewers to come to balanced decisions. This involves focusing on the important issues in the application and adopting those regulatory approaches that will maximize public health benefits while minimizing adverse, unintended consequences.

Regulatory decision-making should be based on the best current science, in the context of each country's public health needs and its medical care system. The scientific rationale for decision-making, including all information used and any dissenting, evidence-based views, should be documented to ensure the integrity of the review process. Decision-making by an RA should be independent of influences beyond public health.

Review strategy

For each specific application, a review strategy – i.e. an approach or plan of action – should be defined and followed by the reviewer or review team to ensure a sound review process. The strategy employed may be shaped by:

- the public health priority of the medical product submitted for review;
- other RAs' action on the product, taking into account any product differences (for example formulation or final container presentation) and any differences in the proposed indications or conditions of use in the local population;
- specific intrinsic and extrinsic factors that are clinically relevant to the population served by the RA; and
- major scientific questions on product safety, efficacy or quality (examples: identification of possible cases of organ toxicity in a patient population with a high background incidence of the same organ disease, use of a new end point for regulatory approval that may not be a direct measure of clinical benefit, or use of conditions for stability testing that are not appropriate for the RA's regional climate). Early identification of complex or precedent-setting issues or areas of high uncertainty in the application can lead to faster and more efficient resolution, based on an early review of the most relevant available data.

Conducting the review

The way in which a review is conducted will depend on available resources. While a multidisciplinary team will provide broader expertise, in some cases an application may be assigned to a single reviewer, seeking input from external experts and/or considering the information and decisions of other RAs as needed.

The review should be evidence-based, taking into account national laws and regulations, regional and international guidelines and, where applicable, monographs and standards. The reviewer should determine the information necessary to approve the product, and consider what further studies (if any) can be left for the post-approval stage without compromising safety.

The model adopted for review may allow for questions to be asked during the review to supplement or clarify the information supplied, until the reviewer is satisfied that enough data have been provided for a conclusion to be reached. In other models, the review is completed on the basis of the information submitted, a list of questions is then sent to the applicant with a time-limit for response, and one further round of assessment of the responses takes place before a decision is made.

The following internal processes may help ensure an efficient, consistent and effective review process:

- periodic meetings to allow consideration of the views of different reviewers;
- peer review, in the context of a co-rapporteur, or a team meeting;
- an internal panel review;
- an external panel review; and
- the involvement of senior management.

Quantifying risks and benefits

The review strategy should enable the reviewer or review team to understand and describe the benefit–risk profile of the medical product, given its indication and context of use. Benefits and risks can be quantified or qualitatively characterized, and the levels of certainty surrounding the benefits and risks should be stated. The review should address generalizability of the data, the clinical significance of the findings and what (if any) additional information may be needed to clarify benefits and risks.

The acceptability of benefits and risks will depend on public health priorities, available alternative therapies, the size and certainty of the treatment effect versus that of the adverse reactions, and possible risk mitigation or benefit enhancement measures (for example responder analyses to identify a population more likely to experience benefits). The benefit–risk profile may vary depending on intrinsic and extrinsic factors that may differ among countries and regions. Moreover, judgement may vary within and among RAs. Evidence-based and public health-focused decision-making principles may serve to mitigate some of the variation.

Review report

The findings and conclusions of the review must be described in a well-documented review report, and the final decision should be conveyed to the applicant. If an RA decides not to grant authorization, a statement of reasons should be provided which details the documents, information and regulatory requirements taken into account in reaching the decision. An appeal mechanism should be provided giving applicants an opportunity to present their case to an independent arbiter.

Some RAs may offer to hold a post-action discussion with the applicant to help improve the quality of future applications.

Lastly the RA may also implement mechanisms for public communication of review outcomes and related information, increasing the transparency of its regulatory actions.

References

1 **Full text of the guideline summarized in this article:** Good review practices: guidelines for national and regional regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report. Geneva, World Health Organization. Technical Report Series No. 992, 2015, Annex 9 (in preparation).
Draft published for comment: Good review practices: guidelines for regulatory authorities. Working document QAS/14.576 Rev.1. August 2014.

2 Guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh report. Geneva, World Health Organization. Technical Report Series, No. 981, 2013, Annex 2.

3 Liu L-L et al. Characterizing Good Review Practices: A Survey Report Among Agencies of APEC Member Economies. Therapeutic Innovation & Regulatory Science, November 2013; 47(6): 678-683. First published on July 19, 2013. doi:10.1177/2168479013494394.

Safety news

Restrictions

Metoclopramide: not for children under one year of age

Canada – The marketing authorization holder, in consultation with Health Canada, has warned that neurological adverse events can occur in children receiving metoclopramide within the daily recommended dosage of 0.5 mg/kg. Metoclopramide is now contraindicated in children less than one year of age in Canada, as a Health Canada review has shown that they are at greater risk of abnormal involuntary movements (extrapyramidal symptoms). In children over one year metoclopramide should only be used if the anticipated benefits clearly outweigh the potential risks.

► Health Canada Advisory, 5 January 2015.

Domperidone: further restrictions

United Kingdom – Further to a recommendation by the European Medicines Agency (EMA) to restrict the use of domperidone to the management of nausea and vomiting due to adverse effects on the heart (see WHO Drug Information Vol. 28, No. 2), domperidone-containing medicines have been restricted in the United Kingdom for supply on prescription only with effect from 4 September 2014. *(1)*

New Zealand – A Medsafe review has concluded that domperidone-containing medicines have a small increased risk of adverse heart effects, which may be higher in patients over 60 years or at total daily doses of more than 30 mg. The manufacturer has decided to reduce the maximum recommended dose from 80 mg to 40 mg daily. *(2)*

Canada – Health professionals have been informed of additional safety information about some cardiac risks associated with domperidone. The medicine is now contraindicated in Canada in patients with prolonged of cardiac conduction intervals, significant electrolyte disturbances, cardiac disease or liver impairment, and those receiving QT-prolonging drugs or potent CYP3A4 inhibitors. Domperidone should be used at the lowest effective dose up to a maximum recommended daily dose of 30 mg and for the shortest possible duration.

► *(1)* Drug Safety Update volume 8 issue 2, September 2014: S1.

(2) Medsafe Safety information, 22 December 2014.

(3) Health Canada Advisory, 20 January 2015.

Nitrofurantoine: revised contraindication in renal impairment

United Kingdom – The Medicines and Healthcare Products Regulatory Agency (MHRA) has recommended to lower the estimated glomerular filtration rate (eGFR) below which nitrofurantoin is contraindicated. Its use should now be allowed in patients with an eGFR of 45 ml/min/1.73m^2 or more (previously: 60 ml/min/1.73m^2). A short course (3 to 7 days) may be used with caution in certain patients with an eGFR of 30–44 ml/

min/1.73m^2 to treat lower urinary tract infection with suspected or proven multidrug-resistant pathogens.

The efficacy of nitrofurantoin in treating and preventing urinary tract infections depends on its renal secretion into the urinary tract. The revised recommendations consider the fact that lower urinary tract pathogens are increasingly resistant to standard therapy (trimethoprim and amoxicillin), and that the widespread use of alternative broad-spectrum antibiotics (cephalosporins and fluoroquinolones) is associated with the risk of *Clostridium difficile* colitis.

► Drug Safety Update volume 8 issue 2, September 2014: A3.

Oral diclofenac: prescription-only in United Kingdom

United Kingdom – Diclofenac 12.5mg and 25mg tablets, formerly available over the counter, have been re-classified as a prescription-only medicines in the United Kingdom with effect from 15 January 2015.

A 2013 Europe-wide review had found that systemic diclofenac is associated with a small increased risk of arterial thromboembolic events, similar to that of COX-2 inhibitors. In the United Kingdom the Commission on Human Medicines (CHM) has reconsidered available evidence and has concluded that the risk of these side effects cannot be ruled out even when the medicine is taken for a short time or at a lower dose. The Commission therefore advised that patients should have a medical review before taking oral diclofenac to make sure it is suitable for them.

► MHRA Press release, 14 January 2015.

Risperidone: not to be used in vascular or mixed-type dementia

Canada – Health Canada has restricted the indication for risperidone (Risperdal®) in dementia to the short-term symptomatic management of aggression or psychotic symptoms in patients with severe dementia of the Alzheimer type unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others. The indication no longer includes the treatment of other types of dementia.

The recommendation is based on available safety information on antipsychotic drugs, indicating a higher risk of cerebrovascular adverse events in patients with mixed and vascular dementia compared to those with dementia of the Alzheimer type.

► Health Canada Advisory, 18 February 2015.

Hydroxyzine: new restrictions

European Union – The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed a review of medicines containing the antihistamine hydroxyzine. These are available in most EU countries for various indications such as treatment of anxiety disorders and sleep disorders, relief of itching caused by urticaria, and as premedication before surgery.

The PRAC considered that hydroxyzine is associated with a small but definite risk of QT interval prolongation and torsade de pointes, which can lead to abnormal heart rhythms and cardiac arrest.

To minimize the risk the Committee has recommended a number of restrictions. Use is not recommended in the elderly. Duration and dosage should be reduced to minimum effective levels. The maximum daily dose should be no more than 100 mg

in adults (50 mg in the elderly if use cannot be avoided), and 2 mg per kg body weight in children up to 40 kg in weight. Use must be avoided in patients who have risk factors for arrhythmias or are taking other medicines associated with QT prolongation; care is needed in patients taking medicines that slow the heart rate or decrease blood potassium levels.

► EMA Press release, 13 February 2015.

Codeine-containing cough and cold medicines: not for children under 12

New Zealand – Medsafe's Medicines Adverse Reactions Committee has recommended to restrict the use of all codeine-containing cough and cold medicines for children, including prescription-only-medicines, to children aged 12 years and over. An EMA review of these medicines started in April 2014 following concerns of morphine toxicity and respiratory depression.

► Minutes of the 160th Medicines Adverse Reactions Committee Meeting, 4 December 2014.

Safety warnings

Linagliptin: possible liver toxicity

Japan – Following reports of hepatic dysfunction in patients treated with linagliptin in Japan, the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan have recommended to update the product information to include this risk.

Health professionals should monitor patients treated with linagliptin for signs of liver dysfunction, including liver enzyme elevations, and should consider stopping linagliptin in case of abnormalities.

► PMDA Summary of investigation results and Revisions of Precautions for linagliptin, 9 January 2015.

See also: Kutoh E. Probable linagliptin-induced liver toxicity: A case report. Diabetes Metab. 2014 Feb;40(1):82-4. doi: 10.1016/j.diabet.2013.09.009.

Apixaban: interstitial lung disease

Japan – The MHLW/PMDA has recommended to revise the product information for the anti-coagulant apixaban (Eliquis®) following reported cases of haemorrhage and bloody sputum suggestive of interstitial lung disease, including suspected interstitial pneumonia in some cases.

► PMDA Summary of investigation results, 17 February 2015.

Chlorhexidine: chemical burns in premature infants

United Kingdom – The MHRA has warned health professionals that alcohol-based and aqueous chlorhexidine solutions used for skin antisepsis prior to invasive procedures can cause chemical burns in neonates. This risk appears to be higher in preterm infants, especially those born before 32 weeks of gestation, and within the first two weeks of life.

Health professionals should remove any soaked materials before proceeding with the intervention. They should not use excessive quantities of chlorhexidine and should not allow the solution to pool in skin folds or under the patient or to drip on any material in direct contact with the patient. Before applying occlusive dressings, care must be taken to remove any excess chlorhexidine.

► Drug Safety Update. Feb 2015; 8 (7): 4.

Testosterone: caution about use in healthy men

United States of America – The U.S. FDA has cautioned about using testosterone products to treat low testosterone levels due to aging. The Agency requires labelling changes to clarify the approved indications of testosterone and to inform health professionals and patients of possible increased risks of heart attack and stroke associated with the use of these products.

Prescription testosterone products are approved in the U.S. only to treat low testosterone levels caused by certain medical conditions. The FDA has become aware that testosterone is being used extensively in attempts to relieve symptoms in men who have low testosterone levels for no apparent reason other than aging. The Agency cautions that the benefit and safety of these medications have not been established in this patient group – even if a man's symptoms seem related to low testosterone – and that some studies in aging men treated with testosterone have reported an increased risk of heart attack, stroke or death. *(1)*

Warnings about the possible cardiac risks associated with testosterone have also been communicated recently by the EMA and New Zealand's Medsafe *(2)*.

► *(1)* FDA Drug safety communication, 3 March 2015.

(2) WHO Drug Information,Vol. 28, No. 4, 2014: 448.

Telaprevir: renal impairment

Japan – The MHLW/PMDA has recommended a revision of the product information for telaprevir, used to treat chronic hepatitis C infection, advising health professionals to consider a reduced initial dose in patients who are at risk of renal impairment.

The recommendation is based on an interim analysis of post-marketing surveillance survey data indicating that a full initial dose, higher age, increased baseline creatinine, and diabetes mellitus or hypertension as comorbidities are risk factors for serious renal impairment in patients treated with telaprevir.

► PMDA Summary of investigation results, 17 February 2015.

Simeprevir: leukopenia and neutropenia

Japan – Following reports of adverse events suggestive of leukopenia and/or neutropenia in patients treated with combination therapy of simeprevir sodium, peginterferon and ribavirin in Japan, the MHLW/PMDA has recommended to revise the package insert for simeprevir. Health professionals should monitor patients for leukopenia and/or neutropenia, and should consider stopping simeprevir in case of severe abnormalities.

► PMDA Summary of investigation results and Revision of Precautions for simeprevir sodium, 9 January 2015.

Mycophenolate mofetil and mycophenolic acid: hypogammaglobulinaemia and bronchiectasis

United Kingdom – In accordance with a review and recommendations by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), the marketing authorization holder of mycophenolate mofetil (CellCept®) in the United Kingdom has informed health professionals of the risk of hypogammaglobulinaemia and the

risk of bronchiectasis associated with the medicine. Mycophenolate mofetil is registered in the United Kingdom to prevent acute transplant rejection and is used off-label in a number of specialties.

Serum immunoglobulin levels should be measured in patients developing recurrent infections and clinical action taken as needed, taking into account the potent cytostatic effects of the drug on B- and T-lymphocytes. In case of persistent respiratory symptoms bronchiectasis or pulmonary fibrosis should be suspected.

► Drug Safety Update volume 8 issue 6, January 2014: 3.

Vemurafenib: pancreatitis

Canada – A new warning about the risk of pancreatitis has been added to the Canadian prescribing information for vemurafenib (Zelboraf®). Vemurafenib is used to treat unresectable or metastatic melanoma with a BRAF mutation in adult patients.

Cases of drug-induced pancreatitis have been reported with the use of vemurafenib both in Canada and elsewhere. The reactions generally occurred during the first two weeks of treatment. Health professionals should suspect pancreatitis in patients taking vemurafenib and presenting with unexplained abdominal pain. If vemurafenib is re-started after an episode of pancreatitis, patients should be closely monitored and a dose modification should be considered.

► Health Canada Advisory, 12 February 2015.

Abiraterone: thrombocytopenia

Japan – The MHLW/PMDA has recommended to revise the product information for abiraterone tablets (Zytiga®), used to treat castration-resistant prostate cancer, to warn health professionals of the risk of thrombocytopenia *(1)*. A safety signal was identified in 2013 from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase™, warranting further investigation *(2)*.

The product information in Japan was updated at the same time to include the risks of hypokalaemia and rhabdomyolysis, two adverse events already reflected in FDA- and EMA-approved product information.

► *(1)* PMDA Revisions of precautions, 2 February 2015.

(2) Herrera Comoglio R. Abiraterone and thrombocytopenia. WHO Pharmaceuticals Newsletter 4, 2013: 20-25.

Ziprasidone: rare but potentially fatal skin reactions

United States of America – The FDA has warned that the antipsychotic drug ziprasidone (Geodon® and generics) is associated with a rare but serious skin reaction known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which can progress to affect other parts of the body and can be fatal.

A warning about this risk has been added to the label of the capsule, oral suspension and injection formulations of this drug. Patients who have a fever with a rash and/or swollen lymph nodes should seek urgent medical care. Health care professionals should immediately stop treatment with ziprasidone if DRESS is suspected.

► FDA Drug safety communication, 11 December 2014.

Donepezil: rhabdomyolysis and neuroleptic malignant syndrome

Canada – Health Canada has communicated new warnings for donepezil, used in the treatment of Alzheimer's disease. This medicine is associated with a risk of two rare but potentially serious conditions: rhabdomyolysis, a rare condition involving the breakdown of muscle tissue, and neuroleptic malignant syndrome (NMS), a very rare life-threatening disorder characterized by a chemical imbalance that affects the nervous, muscular and cardiovascular systems.

Before prescribing donepezil health professionals should assess patients for risk factors for rhabdomyolysis such as: muscular disorders, uncontrolled hypothyroidism, liver or kidney damage, and concomitant use of other medicines that can cause rhabdomyolysis such as statins, antipsychotics, and certain types of antidepressants. Donepezil therapy should be stopped if blood tests show high levels of creatine phosphokinase (CPK), and/or if NMS and/or rhabdomyolysis is diagnosed.

► Health Canada Advisory, 21 January 2015.

Ambroxol/bromhexine: rare severe skin reactions

European Union – The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) – a regulatory body representing EU Member States – has endorsed recommendations to add information about a small risk of severe allergic reactions, including severe cutaneous adverse reactions (SCARs) such as erythema multiforme and Stevens-Johnson syndrome, to the product information for ambroxol- and bromhexine-containing medicines, which are widely used in the EU as expectorants.

The recommendations originated from the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), whose review of the two medicines confirmed the known risk of allergic reactions and identified a small risk of SCARs.

► EMA Press release, 27 February 2015.

Nitric oxide cylinders: faulty valves

European Union – The manufacturer, in cooperation with EMA and national regulatory authorities, has informed health professionals in EU Member States that a defect might cause the valves in some nitric oxide (INOmax®) cylinders to close while in use and before the cylinder is emptied. This abruptly stops gas delivery earlier than expected. Life-threatening rebound effects can occur if the cylinder is not changed immediately.

The defect applies to 400 ppm and 800 ppm cylinders of both the 2 L and 10 L pack sizes. To minimize the adverse reactions health professionals should always have a full spare cylinder loaded onto the delivery device, always use devices with pressure sensor monitors and gas monitor alarms, and when switching cylinders purge the regulator of the second cylinder before connecting it to the device to prevent excessive NO_2 formation. For all patient transfers, even short transfers, back-up cylinders should be kept available.

► MHRA. Drug Safety Update volume 8 issue 7, February 2015: 2.

Unchanged recommendations

Analgesics in pregnancy

United States of America – In response to reports questioning the safety of pain medicines during pregnancy, the FDA has reviewed three types of potential risks: 1) risk of miscarriage following use of prescription non-steroidal anti-inflammatory drugs (NSAIDs) in the first half of pregnancy, 2) risk of birth defects following administration of opioids during the first trimester of pregnancy, and 3) risk of attention deficit hyperactivity disorder in the infant following paracetamol use at any time of pregnancy.

The studies reviewed did not provide sufficiently consistent data to allow reliable conclusions. FDA recommendations on the use of analgesics during pregnancy will remain unchanged.

► FDA Drug safety communication, 9 January 2015.

Manufacturing quality issues

GVK Biosciences: EMA recommends suspensions

European Union – The EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended to suspend some 700 pharmaceutical forms and strengths of medicines authorized in EU Member States based primarily on clinical studies conducted at GVK Biosciences in Hyderabad, India.

An inspection by the French medicines agency ANSM had raised concerns about prolonged and systematic non-compliance with good clinical practice at GVK's Hyderabad site. This does not mean that the medicines concerned are necessarily unsafe for patients, but that reliable data are needed to prove their bioequivalence.

The CHMP has identified those medicines for which insufficient clinical data are available from other sites, and has recommended their suspension unless a national authority considers that a medicine is of critical importance to meet patients' needs in the specific EU Member State. In that case, the marketing authorization holder is given 12 months to submit additional data. *(1)*

Some marketing authorisation holders have requested a re-examination. *(2)*

Switzerland – The Swiss Agency for Therapeutic Products (Swissmedic) has identified three products that are authorized for export from Switzerland on the basis of clinical trials by GVK Biosciences in Hyderabad (India). Swissmedic will now review these authorizations in detail. *(3)*

WHO – Two products prequalified by WHO for purchase by UN agencies have been withdrawn voluntarily by the company from the WHO prequalification list; new data are under assessment for a third prequalified product. *(4)*

► *(1)* EMA Press release, 23 January 2015.
(2) EMA News, 27 February 2015.
(3) Swissmedic Announcement, 6 February 2015.
(4) PQP Information note, 16 January 2015.

Three Indian sites: Canada stops imports

Canada – Health Canada has requested Canadian importers to stop the importation and distribution of products from a number of manufacturing sites in India due to data integrity concerns. Action taken in December 2014 applied to active

pharmaceutical ingredients (APIs) from Dr. Reddy's Laboratories in Srikakulam and to finished drug products from IPCA Laboratories in Pithampur; action taken in January 2015 applied to health products made with APIs from Sri Krishna Pharmaceuticals Ltd. in Hyderabad, India.

In September and October 2014 Health Canada had already imposed import restrictions on pharmaceutical products from some Indian sites, including another IPCA Laboratories facility (see WHO Drug Information, Vol. 28, No. 4).

The import stop is a precautionary measure. Health Canada has not identified a risk to health, nor has it requested a recall of any of the products.

► Health Canada Advisory, 23 December 2014.

Health Canada Advisory, 6 January 2015.

Falsified product alert

Falsified artemether/lumefantrine in West Africa

Following notification from the Global Fund to Fight AIDS, Tuberculosis and Malaria, WHO has received confirmation that falsified packs of artemether/lumefantrine antimalarial tablets have been found in West Africa. The falsified products contain none of the correct active pharmaceutical ingredients. The packs bear the following markings:

- Falsified product purchased in a street market in Abidjan, Côte d'Ivoire:
  Batch number: DYI402542 on the box (secondary packaging)
  DYI402201 on the blister foil (primary packaging)
  Manufacturing date: 07/2013, Expiry date: 06/2016

- Falsified product found in a drug store in Lomé, Togo during an INTERPOL operation:
  Batch number: DYI402541 on the outer bulk pack (tertiary packaging)
  DYI402542 on the box (secondary packaging)
  DYI402201 on the blister foil (primary packaging)
  Manufacturing date: 07/2013, Expiry date: 07/2016

All the above packaging levels bear the ACTm green leaf logo of the Affordable Medicines Facility malaria programme. The writing on the packaging is in English.

WHO is calling for increased vigilance for these specific batches of this product. To report any information concerning these batches, or to report other incidents concerning falsified medicines, please contact rapidalert@who.int.

► WHO Medical Product Alert No. 1/2015, February 2015. (Includes photographs)

Regulatory news

Pre-market assessment

Generics information-sharing pilot expanded

European Union – The EMA is ready to share its assessments of applications also for generic medicines that fall under the EMA's centralized procedure. The information-sharing initiative started in July 2014 using the EU decentralized procedure as a model.

This initiative, under which EU assessment information is shared in real time with collaborating regulatory agencies outside the European Union (EU), is part of the International Generic Drug Regulators Pilot (IGDRP). It brings together 14 regulatory authorities as well as the European Directorate for the Quality of Medicines & Healthcare (EDQM) and WHO as observers.

The first phase of the pilot project will involve the EU, Australia, Canada, Chinese Taipei and Switzerland. Ten applications for generic medicines will be selected initially. Further information has been published on the EMA website.

► EMA news, 19 January 2015.

More about IGDRP: The International Generic Drug Regulators Pilot. WHO Drug Information. 28(1); 2014:3-10.

CFDA issues biosimilars development and evaluation guideline

China – In order to guide and standardize the development and evaluation of biosimilars and promote the sound development of the biomedicine industry, the China Food and Drug Administration (CFDA) has issued the Technical Guideline for Development and Evaluation of Biosimilars (interim), and has specified relevant requirements on the application procedure, registration classification, and application documents of biosimilars.

► CFDA Press release, 5 March 2015.

Pharmacovigilance

EMA upgrades data systems

European Union – The EMA has completed two separate steps to develop its reporting systems in accordance with the EU pharmacovigilance legislation.

Firstly, the Agency has published a guide to support the implementation of a new international ISO standard for reporting of suspected side effects of medicines in Individual Case Safety Reports (ICSRs). The standard will enhance the European EudraVigilance adverse events database. It will bring a globally harmonized format for case reports collected by pharmaceutical companies and regulatory authorities, better quality of data to detect and address medicines safety issues, and stronger personal data protection. The use of the new standard will take effect on 1 July 2016. *(1)*

Secondly, the EMA has launched a centralized electronic repository for periodic safety update reports (PSURs) and their assessment reports. The platform will make it easier for regulators

to access the information and for industry to submit their PSURs electronically. *(2)*

► *(1)* EMA News, 21 January 2015.
(2) EMA News, 26 January 2015.

Canada launches drug safety information web site

Canada – The Government of Canada has launched a new online tool for drug safety information. The Drug and Health Product Register provides consumers with centralized access to information on prescription drugs, including their indications, safety warnings and precautions, common side effects, and adverse reactions that have been reported to Health Canada.

Currently in its pilot phase, the Drug and Health Product Register covers the top 100 prescribed products based on IMS-reported Canadian sales for 2013, together with an additional 250 products that have the same active ingredient(s).

The Drug and Health Product Register is one of several initiatives undertaken as part of Canada's Regulatory Transparency and Openness Framework.

► Government of Canada. News Release, 12 February 2015.

Regulatory oversight

FDA proposes new guidance on compounding

United States of America – The FDA has released for comment five draft documents related to compounding of human drugs. The documents include draft guidance texts on registering an outsourcing facility; adverse event reporting by outsourcing facilities; repackaging of drugs; mixing, diluting and repackaging of biological products; and a draft Memorandum of Understanding between the FDA and the states.

The draft documents are applicable to pharmacies, federal facilities, outsourcing facilities and physicians. The new category of outsourcing facilities was created in 2013 in response to a fungal meningitis outbreak that was linked to contaminated compounded drug products.

► FDA News release, 13 February 2015.

CFDA strengthens good practice guidance for medical devices

China – The China Food and Drug Administration (CFDA) has issued two regulatory good practice documents for medical devices: the revised Good Manufacturing Practice for Medical Devices, effective from 1 March 2015 *(1)*, and the country's first Good Supply Practices for Medical Devices, effective from 12 December 2014 *(2)*.

The two guidance texts are part of strengthened regulation for medical devices, including in vitro diagnostic products, in line with current international regulatory principles.

► *(1)* CFDA Press release, 19 January 2015.
(2) CFDA Press Release, 20 January 2015.

Antibiotics

EMA advice on antibiotics use in animals

European Union – The EMA has published recommendations to minimize antimicrobial resistance arising from the use of antibiotics in veterinary medicines, especially those that are critically important in human medicine, such as fluoroquinolones and third and fourth generation cephalosporins.

Measures are proposed to identify public health risks early in the product life cycle, to monitor antibiotics use and emerging resistance, and to restrict antibiotic use in animals in case of significant public health risks. Tools are also proposed to ban or limit the off-label use in animals of certain antimicrobials authorized only in human medicine.

The advice will serve as input into the discussions that have now started in the European Council and the European Parliament on revising the legislation on veterinary medicines.

► EMA Press release, 19 December 2014.

ECDC/EFSA/EMA first joint report

European Union – The European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) have published their first integrated data analysis on antimicrobial resistance in bacteria from humans and food-producing animals. The report combines data from five monitoring networks that gather information from EU Member States, Iceland, Norway and Switzerland.

In both humans and animals, the analysis found positive associations between consumption of antimicrobials and the corresponding resistance in bacteria for most of the combinations investigated. Despite data limitations, these findings highlight the need to promote the responsible use of antimicrobials in both humans and animals. The report will inform the European Commission's action plan against the rising threats from antimicrobial resistance.

► EMA Press release, 30 January 2015.

Drug availability

Canada announces requirement for reporting of drug shortages

Canada – The Government of Canada is moving towards a mandatory reporting system that will require manufacturers to publicly report actual and anticipated drug shortages. Drug shortages are a complex global problem that can have devastating consequences for certain patients. An advanced warning of upcoming shortages will enable Canadians to proactively work with their healthcare professionals to find alternative treatment options.

While regulations as well as a new, independent third-party website for this reporting are being developed, manufacturers are expected to voluntarily post information on all shortages on the industry-run website www.drugshortages.ca, which was launched in March 2012.

► Government of Canada. News release, 10 February 2015.

EU industry proposal on reducing manufacturing-related medicines shortages

European Union – The pharmaceutical industry, through its associations, has proposed a collaborative contribution to help reduce drug shortages caused by manufacturing, quality and/or GMP issues, a subset of the many diverse root causes for shortages. The proposal encompasses communication principles as well as prevention plans both at system level and at product level *(1)*.

The proposal was made in response to a 2012 EMA Reflection paper on medicinal product supply shortages caused by manufacturing issues *(2)*. Despite existing reporting requirements in the EU and the U.S., drug shortages remain a global challenge. In recent years,

manufacturing- and GMP compliance-related problems have resulted in acute and chronic shortages of important products.

► *(1)* AESGP, EFPIA, EGA, ISPE, PDA and PPTA. Prevention of Drug Shortages Based on Quality and Manufacturing Issues. Final Report. 23 December 2014. A Collaborative Contribution to the European Medicines Agency (EMA) and their Inspectors Working Group (EMA-IWG).

(2) EMA. Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems. EMA/590745/201222. November 2012.

Approvals

Bupropion & naltrexone for weight management

Product name:
EU: Mysimba®; *U.S.:* Contrave®
Dosage form: Prolonged release tablet
Class: Combination of an antidepressant and a drug used in dependence disorders;
ATC code (temporary classification): A08AA62
Approval: EMA, FDA
Use: Weight management of obese adults or overweight adults having certain risk factors, in addition to a reduced-calorie diet and physical activity (prescription-only).
Benefits: Additional option to help manage the weight-related risks for chronic diseases such as diabetes and cardiovascular disease.
Safety information: Safety and tolerability issues have been identified relating to central nervous system and gastrointestinal adverse events, as well as uncertainties about cardiovascular outcomes in the longer term. Both EMA and FDA require some post-marketing monitoring and/or risk management measures for this product.

► EMA Press release, 19 December 2014.
FDA News release, 10 September 2014.

Note: Concerns have been voiced about the safety of this product, considering its potential adverse effects and past regulatory decisions on other weight management products in the EU.

► Prescrire Press release, 19 December 2014.

Liraglutide for weight management

Product name: Saxenda®
Dosage form: Once-daily injection in a pre-filled pen
Class: Glucagon-like peptide-1 (GLP-1) receptor agonist
ATC code: A10BX07
Approval: FDA, EMA
Use: Weight management, in combination with a reduced-calorie diet and physical activity, in obese adults or overweight adults with at least one weight-related health condition (prescription-only).
Benefits: Additional treatment option for chronic weight management to mitigate the risk of chronic health conditions.
Safety information: Some serious side effects have been reported in patients treated with GLP-1-based therapies, including an increased heart rate, pancreatitis, gallbladder disease, renal impairment and suicidal thoughts. In the U.S. the product alsohas a boxed warning against use in patients with a personal or family history of medullary thyroid carcinoma (MTC) or those with multiple endocrine neoplasia syndrome type 2, which predisposes them to MTC. Both EMA and FDA require some post-marketing monitoring and/or risk management measures for this product.
Notes: Liraglutide is already approved in the U.S. and the EU at a lower dose for the treatment of diabetes under the trade name Victoza®.

► FDA News release, 23 December 2014.
EMA Press release, 23 January 2015.

Cangrelor anti-clotting agent

Product name: Kengrexal®
Dosage form: Powder for concentrate for solution for infusion
Class: Platelet aggregation inhibitor
ATC code: B01AC25
Approval: EMA
Use: Co-administered with acetylsalicylic acid ASA, to reduce thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention.
Benefits: Ability to prevent thrombotic cardiovascular events in patients who have not received oral P2Y12 inhibitors before percutaneous coronary intervention.

► EMA/CHMP Opinion, 22 January 2015.

Edoxaban anti-clotting agent

Product name: Savaysa®
Dosage form: Tablets
Class: Anticoagulant; direct Factor Xa inhibitor
Approval: FDA
Use: To reduce the risk of stroke and systemic embolism in patients with atrial fibrillation that is not caused by a heart valve problem, and to treat deep vein thrombosis and pulmonary embolism in patients already treated with a parenteral anticoagulant for five to ten days.
Benefits: Similar efficacy and a lower risk of major bleeding, compared with warfarin.
Safety information: Bleeding is the most serious risk with edoxaban; no treatment has been proven to reverse its anticoagulant effect.
The medicine carries a Boxed Warning on dosing and safety in specific patient groups, including a warning that an alternative anti-clotting agent should be used in atrial fibrillation patients with a creatinine clearance > 95 ml/min (>1.58 ml/s).

► FDA News release, 8 January 2015.

Tolvaptan for rare kidney disease

Product name: Jinarc®
Dosage form: Tablets
Class: Vasopressin-2-receptor antagonist
ATC code: C03XA01
Approval: EMA (orphan designation)
Use: Treatment of autosomal dominant polycystic kidney disease (ADPKD) in patients with normal to moderately reduced kidney function who have rapidly progressing ADPKD.
Benefits: Ability to slow the progression of cyst growth and renal insufficiency in adult patients with ADPKD
Safety information: A pharmacovigilance plan will be implemented with additional monitoring of the risk of liver damage.
Notes: This is the first medicine approved in the EU specifically for the treatment of ADPKD. Tolvaptan is already authorized in the EU under the trade same Samsca® for treating hyponatraemia, although the doses studied in ADPKD are different.

► EMA Press release, 27 February 2015.

Parathyroid hormone to control blood calcium levels in hypoparathyroidism

Product name: Natpara®
Dosage form: Once-daily injection
Class: Parathyroid hormone
ATC code: H05AA03
Approval: FDA (orphan drug designation)
Use: Regulation of blood calcium levels in patients with hypoparathyroidism
Benefits: Alternative treatment option for patients whose calcium levels cannot be controlled on calcium supplementation and active forms of vitamin D.
Safety information: Potential risk of osteosarcoma according to studies in rats. Only available through a restricted programme under a Risk Evaluation and Mitigation Strategy (REMS).

► FDA News release, 23 January 2015.

Approvals

Ceftolozane & tazobactam for certain complicated infections

Product name: Zerbaxa®
Dosage form: Powder for intravenous infusion
Class: Combination of a cephalosporin antibacterial (ceftolozane) and a beta-lactamase inhibitor (tazobactam);
ATC code (temporary classification): J01DI54
Approval: FDA, Qualified Infectious Disease Product (QIDP) designation
Use: Treatment of adults with complicated intra-abdominal infections and complicated urinary tract infections
Benefits: New treatment option for certain types of serious or life-threating infections.
Safety information: The product label includes a warning about decreased efficacy seen in patients with renal impairment.

► FDA News release, 19 December 2014.

Ceftazidime & avibactam for certain complicated infections

Product name: Avycaz®
Dosage form: Fixed-dose combination drug for injection.
Class: Combination of a previously approved cephalosporin antibacterial (ceftazidime). and a new beta-lactamase inhibitor (avibactam).
Approval: FDA (priority review, Qualified Infectious Disease Product, QIDP)
Use: Treatment of complicated intra-abdominal infections in combination with metronidazole, and of complicated urinary tract infections including pyelonephritis, in adult patients who have limited or no alternative treatment options.
Benefits: Treatment option when there are limited or no alternative antibacterial drugs for treating a patient's infection. Use of this product is reserved to such situations.
Safety information: Serious skin reactions and anaphylaxis may occur in patients with penicillin allergies.
FDA News release, 25 February 2015.

Finafloxacin for outer ear infection

Product name: Xtoro®
Dosage form: Otic suspension
Class: Fluoroquinolone
Approval: FDA
Use: Treatment of acute outer ear infection caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*.
Benefits: New antibacterial medicine with proven efficacy for the target conditions.

► FDA News release, 17 December 2014.

Peramivir for influenza

Product name: Rapivab®
Dosage form: Single-dose intravenous injection
Class: Neuraminidase inhibitor
Approval: FDA
Use: Treatment of uncomplicated influenza in adults who have had symptoms of influenza for no more than two days.
Benefits: Single-dose intravenous treatment option for uncomplicated influenza.
Safety information: Risk of rare but serious skin or hypersensitivity reactions such as Stevens-Johnson syndrome and erythema multiforme. Patients with influenza may be at an increased risk of hallucinations, delirium and abnormal behaviour early in their illness and should be monitored.
Note: This is the first FDA-approved neuraminidase inhibitor for intravenous administration.

► FDA News release, 22 December 2014.

Lamivudine & raltegravir

Product name: Dutrebis®
Dosage form: Film-coated tablets
Class: Antivirals for HIV infection
ATC code: J05AR16
Approval: EMA
Use: Treatment of HIV infection
Benefits: Improved dosing regimen with a reduced daily pill burden.

► EMA/CHMP Opinion, 22 January 2015.

Meningococcal serogroup B vaccine

Product name: Bexsero®
Dosage form: Suspension for injection in a pre-filled syringe
Class: Meningococcal serogroup B vaccine
ATC code: J07AH09
Approval: FDA (accelerated approval; breakthrough therapy)
Use: Prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in individuals 10 through 25 years of age.
Notes: Bexsero® is the second licensed meningococcal group B vaccine in the U.S., after Trumenba® licensed in October 2014.

► FDA News release, 23 January 2015.

Human Papillomavirus 9-valent Vaccine, Recombinant for prevention of certain cancers

Product name: Gardasil 9®
Dosage form: Suspension for intramuscular injection
Class: Human Papillomavirus 9-valent Vaccine, Recombinant
Approval: FDA
Use: Prevention of certain diseases caused by nine types of Human Papillomavirus (HPV)
Benefits: Added protection against five additional HPV types—31, 33, 45, 52 and 58— which cause approximately 20 percent of cervical cancers and are not covered by previously FDA-approved HPV vaccines.

► FDA News release, 10 December 2014.

Sabin inactivated polio vaccine (sIPV)

Product name: Ai Bi Wei (brand name in China)
Dosage form: Injection
Class: Inactivated poliomyelitis vaccine (IPV), Sabin strain
Approval: China Food and Drug Administration (CFDA)
Use: Vaccination against poliomyelitis
Benefits: This vaccine will play a critical role for the eradication of poliomyelitis in China. *(1)*
Note: This is the second Sabin IPV to be licensed worldwide. The Global Polio Eradication Initiative's Eradication and Endgame Strategic Plan 2013–18 calls for IPV to be introduced into immunization programmes. The CFDA-approved IPV vaccine could play an important role in global polio eradication if it is shown to meet international quality standards. In October 2013 the first produced in China – a vaccine against Japanese encephalitis – achieved WHO prequalification, making it acceptable for procurement by international organizations such as UNICEF and the GAVI Alliance. *(2)*

► *(1)* CFDA Press release, 16 January 2015.

(2) China enters the global vaccine market [News]. Bulletin of the World Health Organization 2014;92:626-627. doi: http://dx.doi.org/10.2471/BLT.14.020914

Ceritinib for certain lung cancers

Product name: Zykadia®
Dosage form: Hard capsule
ATC code: L01XE28
Class: Protein kinase inhibitor
Approval: EMA (conditional marketing authorization – requirement for further results from ongoing studies and a comparative phase III study within the next three years)
Use: Treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer previously treated with crizotinib
Benefits: Treatment option for a high unmet medical need in patients previously treated with crizotinib, as treatment options are currently very limited.
Safety information: The most serious adverse reactions are hepatotoxicity,

gastrointestinal effects, QT interval prolongation, bradycardia, interstitial lung disease/pneumonitis and hyperglycaemia.

► EMA Press release, 27 February 2015.

Nivolumab for advanced melanoma and lung cancer

Product name: Opdivo®
Dosage form: Injection solution for intravenous infusion
Class: Monoclonal antibody, PD-1 blocker
ATC Code (temporary classification): L01XC17
Approval: FDA (breakthrough therapy, priority review and orphan product designations)
Use: Treatment of unresectable or metastatic melanoma that no longer responds to other medicines. *(1)*
Benefits: Additional treatment option for patients previously treated with ipilimumab and – in the case of patients whose tumours express a BRAF V600 mutation – a BRAF inhibitor.
Subsequently approved use: Treatment of advanced (metastatic) squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy. *(2)*
Safety information: The most serious adverse effects are severe immune-mediated side effects involving healthy organs, including the lung, colon, liver, kidneys and hormone-producing glands.

► *(1)* FDA News release, 22 December 2014.
(2) FDA News release, 4 March 2015.

Lenvatinib for certain progressive thyroid cancers

Product name: Lenvima®
Dosage form: Capsules
Class: Kinase inhibitor
ATC Code (temporary classification): L01XE29
Approval: FDA (priority review)
Use: Treatment of patients with progressive, differentiated thyroid cancer whose disease progressed despite receiving radioactive iodine therapy
Benefits: New therapy to help slow the progression of differentiated thyroid cancer
Safety information: Lenvatinib may cause serious side effects, including cardiac failure, blood clot formation, liver damage, kidney damage, gastrointestinal perforation or fistula formation, QT interval prolongation, hypocalcaemia, the simultaneous occurrence of headache, confusion, seizures and visual changes (Reversible Posterior Leukoencephalopathy Syndrome), serious bleeding, risks to an unborn child if a patient becomes pregnant during treatment, and impairing suppression of the production of thyroid-stimulating hormone.

► FDA News release, 13 February 2015.

Palbociclib for advanced breast cancer

Product name: Ibrance®
Dosage form: Capsules
Class: Antineoplastic agent; cyclin-dependent kinase (CDKs) 4 and 6 inhibitor
Approval: FDA (accelerated approval, breakthrough therapy)
Use: Treatment of certain metastatic breast cancers in postmenopausal women who have not yet received an endocrine-based therapy. Palboclicib is to be used in combination with letrozole (Femara®)
Benefits: New treatment option for certain types of metastatic breast cancer.

► FDA News release, 3 February 2015.

Safinamide for Parkinson's disease

Product name: Xadago®
Dosage form: Film-coated tablets
Class: Selective and reversible monoamine oxidase B (MAO-B) inhibitor
Approval: EMA
Use: Treatment of adult patients with idiopathic Parkinson's disease as add-on therapy

Benefits: Ability to prolong the times during which symptoms are adequately controlled ("on" times) in patients with motor fluctuations receiving L-dopa alone or in combination with other medications for Parkinson's disease.

▶ EMA/CHMP Opinion, 19 December 2014.

Autologous limbal stem cells for limbal stem cell deficiency due to burns to the eyes

Product name: Holoclar®

Living tissue equivalent intended to be transplanted in the affected eye(s), made from a biopsy taken from the patient's cornea and grown in cell culture.

Class: Ex-vivo expanded autologous human corneal epithelial cells containing stem cells, ophthalmological product
ATC code: S01XA19

Approval: EMA (orphan designation)

Use: Treatment of moderate to severe limbal stem cell deficiency due to physical or chemical burns to the eye(s) in adults.

Benefits: Ability to repair the damaged ocular surface, to improve or resolve symptoms of pain, photophobia and burning, and to improve the patient's visual acuity.

Note: This is the first stem-cell therapy recommended for approval in the EU.

▶ EMA News, 19 December 2014.

Extensions of indications

Related reading: *Adaptive licensing pathways*, page 32.

Product	Newly approved indication	Reviewing authority reference
Lenalidomide (Revlimid®) Hard capsule	Continuous treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.	▶ EMA/CHMP Opinion, 18 December 2014.
Bevacizumab (Avastin®) Concentrate for solution for intravenous infusion	In combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix.	▶ EMA/CHMP Opinion, 26 February 2015.
Paclitaxel (Abraxane®) Powder for suspension for infusion	In combination with carboplatin, first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.	▶ EMA/CHMP Opinion, 22 January 2015.

Continued

Extensions of indications

Continued

Product	Newly approved indication	Reviewing authority reference
Ibrutinib (Imbruvica®) Capsules	Treatment of Waldenström's macroglobulinaemia, a rare form of cancer that begins in the body's immune system. Note: This is the first drug approved worldwide specifically for treatment of Waldenström's macroglobulinaemia.	FDA (breakthrough therapy, priority review, and orphan product designation) ▶ FDA News release, 29 January 2015.
Bortezomib (Velcade®) Powder for solution for injection	In combination with rituximab, cyclophosphamide, doxorubicin and prednisone treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.	▶ EMA/CHMP Opinion, 18 December 2014.
Ramucirumab (Cyramza®) Concentrate for solution for infusion	Treatment of metastatic non-small cell lung cancer, in combination with docetaxel.	FDA (priority review) ▶ FDA News release, 12 December 2014.
Lisdexamfetamine dimesylate (Vyvanse®) Capsules	Treatment of binge eating disorders in adults - first FDA-approved medication to treat this condition. Safety information: The most serious risks include psychiatric problems and heart complications. Lisdexamfetamine is a Schedule II controlled substance in the U.S. because of its high potential for abuse.	FDA (priority review) ▶ FDA News release, 30 January 2015.
Ranibizumab (Lucentis®) Injection	Treatment of diabetic retinopathy in patients with diabetic macular oedema. The drug is intended to be used together with appropriate interventions to control blood sugar, blood pressure and cholesterol. Safety information: Endophthalmitis and retinal detachments are the two most serious side effects associated with ranibizumab.	FDA (breakthrough therapy designation, priority review) ▶ FDA News Release, 6 February 2015.

Continued

Continued

Product	Newly approved indication	Reviewing authority reference
Palonosetron (Aloxi®) Solution for injection	Prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy, and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in paediatric patients 1 month of age and older.	▶ EMA/CHMP Opinion, 22 January 2015.

Labelling changes

Diabetes pen devices for single-patient use only

Product: Multi-dose diabetes pen devices

Regulatory authority: FDA

Labelling change: The FDA requires that pens and packaging containing multiple doses of insulin and other injectable diabetes medicines display a warning label stating "For single patient use only." Additional warnings against sharing pens will also be added to the prescribing information and to the patient Medication Guides, Patient Package Inserts, and Instructions for Use.

Note: Even if the needle is changed insulin pens and pens for other injectable diabetes medicines should never be shared among patients, as blood may be present in the pen after use. The requirement was introduced to reduce the serious risk of infection spread through sharing of multi-dose diabetes pen devices.

▶ FDA Drug safety communication, 25 February 2015.

Xpert® MTB/RIF test can guide decisions on ending patient isolation

Product name: Xpert® MTB/RIF Assay

Test type: Nucleic acid amplification test to detect *M. tuberculosis* complex and genetic markers for rifampicin resistance.

Regulatory authority: FDA

Labelling change: Revised labelling states that the results from one or two consecutive negative MTB/RIF tests strongly predict the results that would be obtained from acid-fast bacilli smear testing of three sputum specimens collected eight to 24 hours apart. Results from one or two MTB/RIF tests (depending on the specific patient being tested and hospital guidelines) can be used in the decision to remove patients from airborne infection isolation.

Caution: the MTB/RIF test may not detect all patients with active tuberculosis (TB). The FDA advises that healthcare workers should also continue to follow current CDC guidelines to collect consecutive sputum specimens for TB culture testing, even if results from MTB/RIF testing are negative.

▶ FDA News release, 12 February 2015.

Publications and events

Access to treatment

Adaptive licensing pathways

A recent publication takes a look at the environmental changes that may make adaptive licensing pathways the approach of the future.

The concept of adaptive licensing foresees an early approval of a medicine for a restricted patient population, based on small initial clinical studies. The initial marketing authorization is then progressively adapted to make the medicine accessible to broader patient populations, based on data gathered from its use and from additional studies.

Key drivers that could make adaptive pathways the preferred approach in future include: growing patient demand for timely access to promising therapies in particular where there are unmet medical needs; identification of subgroups of patients who are likely to respond to certain medicines better than others; rising payer influence with calls for a more targeted use of medicines to increase their therapeutic value; and pressure on industry and investors to make drug development sustainable by targeting smaller, better defined patient populations to bring medicines forward at a lower initial cost.

- EMA News, 15 December 2014.

  Eichler HG, Baird LG, Barker R. et al. From adaptive licensing to adaptive pathways: Delivering a flexible life-span approach to bring new drugs to patients. Clin Pharmacol Ther. Accepted Article, 12 December 2014. doi: 10.1002/cpt.59

Appraisal of expensive medicines

An editorial in the *Bulletin of the World Health Organization* presents the case for a global forum to discuss objectivity and equity in access to high-priced drugs.

Increasingly, patients are asking for early access to new drugs, for example to treat cancer. Often these drugs are very expensive. Price-setting is largely a function of the market, and the prices of some recently introduced drugs – for example sofosbuvir – have been questioned.

The authors argue that it is time for a global forum for the development of methods to evaluate available data for early market entry, determine an appropriate initial price, optimize the collection of data from clinical practice, enable independent trials and manage the exit of products that, in practice, are found to be insufficiently effective.

- Hill SR, Bero L, McColl G, Roughead E. Expensive medicines: ensuring objective appraisal and equitable access. Bulletin of the World Health Organization 2015;93:4. doi: http://dx.doi.org/10.2471/BLT.14.148924

BRICS Ministers tackle priority diseases

Brasília – At their Meeting held on 4-5 December 2014, Ministers of Health from Brazil, Russia, India, China and South Africa (BRICS) reaffirmed their commitment to fight priority diseases.

They committed to ambitious tuberculosis targets and approved the development of a plan to achieve universal access to first line

anti-tuberculosis medicines in BRICS and low- and middle-income countries. The plan will include common approaches to promote research and innovations on tuberculosis diagnostics and treatment, share technologies, and identify manufacturing capacities and means of financing.

The Ministers also committed to ambitious HIV treatment targets to end the AIDS epidemic as a global threat by 2030, and they reaffirmed their support to initiatives to overcome barriers in access to medicines.

They further expressed their support for WHO global action plans to stop the Ebola outbreak, to fight neglected tropical diseases, to reduce antimicrobial resistance, and to fight non-communicable diseases.

► IV Meeting of the BRICS. Joint Communiqué. 5 December 2014.

LDCs request extension of intellectual property rights waiver for medicines

Geneva – At the World Trade Organization (WTO) intellectual property committee meeting held on 24-25 February 2015 a group of least-developed countries (LDCs) have proposed to extend the current waiver to intellectual property rights enforcement for pharmaceutical products past the deadline of 2016, until they are no longer considered LDCs.

LDCs are disproportionately exposed to the health risks associated with poverty. In its statement the group notes that "patent protection contributes to high costs, placing many critical treatments outside the reach of LDCs".

► WTO News, 24 February 2015.
IP Watch post, 25 February 2015.

Medicines Patent Pool signs licensing agreements for paediatric antiretrovirals

Geneva – The Medicines Patent Pool (MPP) has signed two new licensing agreements for HIV paediatric formulations, enabling pharmaceutical companies to develop, manufacture and sell low-cost product versions in countries with high disease burdens.

An agreement has been signed with AbbVie for lopinavir and ritonavir, covering 102 countries of which more than 65 are classified as middle-income nations. Moreover, provisions in the agreement permit manufacture and distribution in countries where AbbVie does not hold patents, such as in India where the company has withdrawn its patent applications for both lopinavir and ritonavir. *(1)*

An agreement has also been signed with MSD, known as Merck in the United States and Canada. The agreement is for paediatric formulations of raltegravir and covers 92 low- and middle-income countries. Raltegravir fills an important gap in the care of children who fail on their first-line HIV regimens. *(2)*

The licenses will support the work of the recently launched Paediatric HIV Treatment Initiative (PHTI) to develop better adapted medicines for children living with the virus.

The MPP cooperates with the WHO Prequalification of Medicines Programme to ensure that medicines made with MPP licences meet international quality and safety standards and are acceptable for UN procurement.

► *(1)* MPP Press release, 1 December 2014.
(2) MPP Press release, 24 February 2015.

Anti-TB drug donation agreed

Geneva – The United States Agency for International Development (USAID) and the Johnson & Johnson affiliate Janssen Therapeutics have signed a memorandum of understanding to provide 30 000 treatment courses of the newly developed medicine bedaquiline worth US$ 30 million for free through USAID's programmes. The medicine will be distributed to nearly 100 eligible low- and middle-income countries over four years. Eligibility criteria will be developed over the coming months.

Bedaquiline is the first new anti-tuberculosis drug developed in four decades. It is effective against strains of tuberculosis that are resistant to two or more antibiotics.

The Executive Secretary of the Stop TB Partnership, Dr Ditiu, noted that the community should use this opportunity wisely to save lives, and that the deal sets a precedent for collaboration between pharmaceutical companies and international organizations to tackle drug-resistant tuberculosis.

▶ USAID Press release, 11 December 2014. Stop TB Partnership News, 12 December 2014.

Product development

New anti-tuberculosis medicine starts clinical testing

New York – The Global Alliance for TB Drug Development (TB Alliance) has announced the start of the first human trial of a new tuberculosis drug candidate, a next-generation nitroimidazole designated TBA-354. It is the first new TB drug candidate to begin a Phase I clinical trial since 2009.

TBA-354 was identified in studies conducted by TB Alliance in collaboration with the University of Auckland and University of Illinois-Chicago. In preclinical studies, TBA-354 demonstrated more potent anti-bactericidal and sterilizing activity than pretomanid, another nitroimidazole drug that is currently being tested as a component of other novel regimens in multiple clinical trials.

The TB Alliance is a not-for-profit organization dedicated to finding faster-acting and affordable drug regimens to fight tuberculosis through innovative science with support from partners around the globe.

▶ TB Alliance News release, 18 February 2015.

Disease updates

Ebola: an unforgiving virus

Geneva – One year after the first Ebola cases emerged in Guinea, WHO has released a series of 14 papers that take an in-depth look at different aspects of the epidemic *(1)*.

Vaccines

As the epidemic begins to ebb, efforts to develop, test, and approve Ebola vaccines are followed through as they will have a significant impact on the further evolution. Two vaccines are at an advanced stage of developmen; large volumes of vaccine doses could become available from early 2015 although deployment and further evaluation in the aftermath of the outbreak will be demanding *(2)*. The first Phase III trial was launched in Guinea in March 2015 *(3)*. A third vaccine candidate is in Phase I trials and a number of others are under development *(4)*.

Treatments

Convalescent blood therapies and medicines have been further evaluated.

Two medicines approved for other uses – favipiravir and brincidofovir – warrant further investigation in clinical trials in affected countries *(2)*. The EMA has reviewed seven medicine candidates to treat Ebola, and has found that available evidence is not sufficient to draw conclusions on their safety and efficacy *(5)*.

Diagnostics

WHO has established an emergency quality assessment mechanism for in vitro diagnostics (IVDs) for Ebola Virus Disease. The mechanism aims to identify products that are acceptable for procurement by UN organizations and other partners while further data are being developed. In November 2014 WHO accepted the first Ebola in vitro diagnostic product under this mechanism; the first rapid test followed in February 2015. Other products are under assessment.

WHO is working with the Foundation for Innovative New Diagnostics (FIND), Médecins Sans Frontières (MSF), manufacturers and regulators to guide the development of new tests. *(6)*

The way forward

Four main lessons have been learned from this largest and longest Ebola outbreak in history: Firstly, resilient health systems must be built in all countries to absorb the shocks of future epidemics and climate changes. Secondly, vigilance and preparedness make a huge difference. Thirdly, a host of control measures must be coordinated to fight disease outbreaks, and lastly, community engagement is essential for an effective response. *(7)*

At a special session held in January 2015 the WHO Executive Board unanimously adopted a comprehensive resolution on next steps to end the Ebola outbreak and on what is needed in the longer term for the world to respond to health emergencies under WHO's leadership. *(8)*

► *(1)* WHO. One year into the Ebola epidemic: a deadly, tenacious and unforgiving virus. January 2015.

(2) WHO. Modernizing the arsenal of control tools: Ebola vaccines. January 2015.

(3) WHO/MSF/NIPH Joint news release, 5 March 2015.

(4) WHO Essential medicines and health products. WHO Ebola R&D Effort – vaccines, therapies, diagnostics [web page]. 30 January update.

(5) EMA Press release, 16 December 2014.

(6) WHO. In vitro diagnostics and laboratory technology. Emergency Use Assessment and Listing (EUAL) Procedure for Ebola Virus Disease (IVDs) [web page].

(7) WHO. Ebola response: what needs to happen in 2015. January 2015.

(8) WHO Executive Board Special Session on Ebola. EBSS3.R1. Ebola: ending the current outbreak, strengthening global preparedness and ensuring WHO's capacity to prepare for and respond to future large-scale outbreaks and emergencies with health consequences. 25 January 2015.

Non-communicable diseases: preventable early deaths

Geneva – WHO has launched its global status report on noncommunicable diseases (NCDs) for 2014. The report calls for government action to reduce the annual toll of 16 million premature deaths – before the age of 70 – from heart and lung diseases, stroke, cancer and diabetes. 82% of these deaths occur in low- and middle-income countries.

The report outlines a plan with nine voluntary global targets to address key NCD risk factors. It identifies "best buy" cost-effective preventive interventions to reduce tobacco use, salt intake, physical inactivity, high blood pressure

and harmful use of alcohol. Targets are also set for access to drug therapy and counselling – including glycaemic control – to prevent heart attacks and strokes, and for availability of affordable basic technologies and essential medicines – including generics – to treat major NCDs in both public and private facilities.

► WHO News release, 19 January 2015.

Tuberculosis: further to go

Geneva – Improved data show that there are almost half a million more tuberculosis cases worldwide than previously estimated. According to the WHO Global Tuberculosis Report 2014 *(1)* nine million people developed tuberculosis in 2013, and 1.5 million died. Encouragingly, incidence and mortality rates are still falling, and an estimated 37 million lives have been saved through effective diagnosis and treatment since 2000.

Nevertheless a staggering number of lives continue to be lost to this curable disease. Around three million tuberculosis cases are still being missed by health systems each year because they are either not diagnosed or not reported.

The multidrug-resistant tuberculosis (MDR-TB) crisis continues, with severe epidemics in some regions and low treatment success rates in many settings around the world. Extensively drug-resistant tuberculosis (XDR-TB), which is even more expensive and difficult to treat than MDR-TB, has now been reported in 100 countries. The report includes a supplement that marks 20 years of anti-TB drug-resistance surveillance and outlines the MDR-TB response and priority actions.

The authors of a comment in *The Lancet* *(2)* have called on all governments and donors to increase their funding for urgent, swift, and visionary action to reach the target defined in the WHO Global TB strategy, which is to eliminate tuberculosis as a public threat by 2035.

► *(1)* WHO. Global Tuberculosis Report 2014.

(2) Zumla A et al. The WHO 2014 Global tuberculosis report – further to go. The Lancet Global Health , Volume 3 , Issue 1 , e10 - e12.

Malaria: fragile gains

London – The World Malaria Report 2014, launched in the United Kingdom Houses of Parliament in December 2014, shows some encouraging results. The number of people dying from malaria has fallen dramatically since 2000, and malaria cases are also steadily declining. Between 2000 and 2013, the malaria mortality rate decreased by 47% worldwide and by 54% in the WHO African Region, where about 90% of malaria deaths occur.

While biological and technical challenges remain, a strong pipeline of innovative new products has the potential to transform malaria control and elimination. However, despite a threefold increase since 2005, funding to combat malaria is still only around half of the US$ 5.1 billion needed to achieve global targets. *(1)*

Adequate resourcing is particularly important to contain the parasite resistance to antimalarials that now affects five Asian countries. A recent study found that resistant strains have spread throughout Myanmar and have reached the border with India. If resistant malaria spreads to Africa, millions of lives could be at risk. *(2)*

► (1) WHO News release, 9 December 2014.

(2) Tun KM et al. Spread of artemisinin-resistant *Plasmodium falciparum* in Myanmar: a cross-sectional survey of the K13 molecular marker. Lancet Infect

Dis 2015. Published online, 20 February 2015. http://dx.doi.org/10.1016/S1473-3099(15)70032-0.

HIV: fast track targets

Geneva/Los Angeles – A UNAIDS flagship report launched during an event at the University of California, Los Angeles (UCLA) in November 2014 shows how the world can now build on past achievements to end the AIDS epidemic as a global health threat.

By the end of 2013, 35 million people were living with HIV worldwide. New HIV infections in 2013 were estimated at 2.1 million, which was 38% lower than in 2001. The number of AIDS-related deaths also continues to decline, with 1.5 million people dying of AIDS-related causes in 2013, down 35% from the peak in 2005.

There is a global consensus to aim for 90% of people living with HIV knowing their HIV status, 90% of people who know their status receiving treatment and 90% of people on HIV treatment having a suppressed viral load thus reducing the risk of transmission. Other targets include reducing the annual number of new HIV infections by more than 75%, to 500 000 in 2020, and achieving zero discrimination. Investments will be critical in achieving these targets. Particular efforts are needed in the 30 countries that together account for 89% of new HIV infections worldwide, requiring significant commitments from both national and international sources.

► UNAIDS Press release, 18 November 2014.

Neglected tropical diseases: domestic investments needed

Geneva – WHO has released its report *Investing to overcome the impact of neglected tropical diseases*. The Organization urges affected countries to scale up their investment in tackling 17 neglected tropical diseases in order to improve the health and well-being of more than 1.5 billion people. This investment would represent as little as 0.1% of current domestic expenditure on health in affected low- and middle-income countries for the period 2015-2030.

Neglected tropical diseases cause blindness, disfigurement, permanent disability and death. While good progress has been made towards eliminating some of them, others are gaining ground because of rapid and unplanned urbanization, population movement and environmental change. Dengue is one of them: it is now present in more than 150 countries. The report outlines an investment case and essential package of interventions for each of the 17 neglected tropical diseases targeted by WHO.

► WHO News release, 19 February 2015.

WHO matters

MQAS procurement guidelines now available in French

Geneva – The 2014 revisions of two procurement-related WHO guidelines are now also available in French: The *Model quality assurance system for procurement agencies (1)* and the *Assessment tool based on the model quality assurance system for procurement agencies: aide-memoire for inspection (2)*.

These guidelines are widely used by international organizations to assure the quality of the health products that they purchase or finance globally.

► *(1)* Système modèle d'assurance de la qualité pour agences d'approvisionnement. Dans : WHO Expert Committee on

Specifications for Pharmaceutical Preparations, forty-eighth report. Genève, OMS, 2014 (Série de rapports techniques de l'OMS, N° 986), Annexe 3.

(2) Outil d'évaluation des AA fondé sur le Système modèle d'assurance de la qualité pour AA: aide-mémoire pour les inspections. Dans : WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-eighth report. Genève, OMS, 2014 (Série de rapports techniques de l'OMS, N° 986), Annexe 4.

Note: To complement the two WHO guidelines a self-assessment tool on compliance with MQAS principles has been published in WHO Drug Information, Vol. 28, No. 4). An Excel version is available from druginfo@who.int.

Do you manufacture these APIs? We are interested in you

The World Health Organization's prequalification scheme gives free help to manufacturers of selected active pharmaceutical ingredients (APIs), medicines and vaccines who want to boost their standards and access international markets.
Read this article for more details:

► in-Pharma Technologist.com. Free Newsletter. Article from CPHI India, 2014. Fiona Barry, 4 December 2014.

Note: The 7th Invitation for API manufacturers to submit an Expression of Interest (EOI) for evaluation of their API by the WHO Prequalification Team - Medicines is available at: http://apps.who.int/prequal/info_applicants/eoi/API-EOI_V7_1.pdf.

New phase of WHO's external quality control laboratory scheme

The important role of QC laboratories

Quality of medicines is a major public health challenge, particularly in light of the cross-border health-related issues and the international dimensions of trade. Within the wide range of quality assurance measures that are needed to help ensure that quality medicines reach the patient, quality control has traditionally been one of the key elements. Pharmaceutical quality control laboratories play a major role in protecting patients from harm.

Quality control (QC) testing is complex. Errors are not only costly but may jeopardize patient safety. Patients may receive ineffective or even harmful medicines if true quality deficiencies are not identified. Conversely, if non-conforming results are falsely interpreted as quality failures, expensive medicines may be returned or destroyed, potentially leaving patients without life-saving treatment until the products are replaced at sometimes enormous additional costs.

Given these high stakes, trust in a QC laboratory's capabilities is essential for all stakeholders who request its services.

New phase of EQAAS

WHO is pleased to announce Phase 6 of its External Quality Assurance Assessment Scheme (EQAAS) at preferential fees far below cost for participants from lower- and middle-income countries. In order to enhance the efficiency and save costs, two studies will be carried out for each shipment. Fees are based on the World Bank classification of income and are as follows:

- Laboratories in low-income countries: US$ 1000
- Laboratories in middle-income countries: US$ 2000
- Laboratories in high-income countries: US$ 4000

The above fees cover shipment of test samples for two studies, together with the study protocols and the subsequent statistical evaluation of the submitted results. WHO informs the laboratories

about their performance and provides additional guidance for improving their capabilities. The scheme is set out in close cooperation with related WHO programmes, including the programme dealing with the prequalification of QC laboratories.

Funding

International donors may be approached for funding of participation in the EQAAS. The Global Fund to Fight AIDS, Tuberculosis and Malaria encourages grant applicants to include this item in their applications for funding. The Global Fund requires grant recipients to arrange systematic random QC testing of products throughout the in-country supply chain for medicines worth about US$ 600 million delivered to grant-funded programmes every year. It also funds large quantities of laboratory equipment and reagents. Other donors have similar policies.

WHO invites laboratories to participate in EQAAS Phase 6 studies. To ensure continued assistance to laboratories in Member States, WHO will offer advice on possible funding sources through WHO country projects for laboratories in developing countries that have no means to recuperate the fee, and for whom the fee represents an obstacle for participation.

More about EQAAS

WHO at present offers the only global, independent scheme to measure laboratories' QC testing capabilities. The EQAAS was established by WHO in 2000 at the request of the Global Fund as a mechanism to maximize health benefits achieved with grant investments in pharmaceuticals and laboratory supplies.

The EQAAS has proven to be a major asset to WHO Member States. More than 60 laboratories across WHO's six regions, many of them in Africa, have participated in its past comparative external assessment studies. Participation in such studies is mandatory according to WHO good practices for pharmaceutical quality control laboratories and for ISO 17025 accreditation.

▶ For more information and expression of interest to participate in this new phase of WHO's QC laboratory scheme, please contact WHO at: EQAAS@who.int.

WHA resolutions now on official record

Geneva – The Sixty-seventh World Health Assembly (WHA), held in May 2014, adopted a total of 25 resolutions, including two with particular relevance to medicines regulation. Resolution WHA67.20 urges Member States and WHO to work together to strengthen national regulatory systems around the world, while Resolution WHA67.21 emphasizes the need for updated norms and regulations for biotherapeutic and biosimilar products. This new generation of medicines holds great promise if they can be put within the reach of all who need them.

The final wording of the Sixty-seventh World Health Assembly's resolutions is now available in WHO's official online records of resolutions and decisions (http://apps.who.int/gb/or/). The two above-mentioned resolutions are reproduced on the following pages for easy reference.

▶ World Health Assembly. Resolution WHA67.20. Regulatory system strengthening for medical products. 24 May 2014.

▶ World Health Assembly. Resolution WHA67.21. Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety and efficacy. 24 May 2014.

WHA Resolutions

WHA67.20: Regulatory system strengthening for medical products[1]

The Sixty-seventh World Health Assembly,

Having considered the report on regulatory system strengthening; [2]

Welcoming the efforts of the Director-General, and recognizing the pivotal role that WHO plays in supporting countries in strengthening their regulatory systems of medical products for human use,[3] and in promoting equitable access to quality, safe, efficacious and affordable medical products;

Recalling the Constitution of the World Health Organization, which affirms that the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition;

Recalling also United Nations General Assembly resolution 67/81 on global health and foreign policy, which, inter alia, recognized the importance of universal coverage in national health systems, especially through primary health care and social protection mechanisms, in the provision of access to health services for all, in particular for the poorest segments of the population;

Recalling further resolutions WHA45.17, WHA47.17, WHA52.19, WHA54.11, WHA59.24, WHA63.12 and WHA65.19, all of which encompass aspects of the need to promote the quality, safety, efficacy and affordability of medicines, including blood products;

Reaffirming resolution WHA65.19 on substandard/spurious/falsely-labelled/falsified/counterfeit medical products, which establishes a new Member State mechanism for international collaboration, from a public health perspective, excluding trade and intellectual property considerations, to prevent and control substandard/spurious/falsely-labelled/falsified/counterfeit medical products and to promote access to affordable, safe and quality medical products;

Recognizing that effective regulatory systems are an essential component of health system strengthening and 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 to safe, effective and quality medical products;

Recognizing also that effective regulatory systems are necessary for implementing universal health coverage, responding to the dual burden of infectious and noncommunicable diseases, and achieving Millennium Development Goal 4 (Reduce child mortality), Goal 5 (Improve maternal health) and Goal 6 (Combat HIV/AIDS, malaria and other diseases);

Aware that health systems need to promote access to essential medical products and that, in order to ensure universal access to health care, rational use of medicines and the sustainability of health systems, urgent action is needed by the international community, Member States and relevant actors in health systems;

Very concerned by the impact on patients of medical products of compromised quality, safety and efficacy, in terms of poisoning, inadequate or no treatment, contributions to drug resistance, the related economic burden, and erosion of public trust in the health system;

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1 See Annex 6 for the financial and administrative implications for the Secretariat of this resolution.

2 Document A67/32.

3 For the purpose of this resolution, medical products include medicines, vaccines, diagnostics and medical devices.

Aware of the regulatory challenges presented by the ever-increasing complexities of medical product supply chains and welcoming the work plan of the Member State mechanism on substandard/
spurious/falsely-labelled/falsified/counterfeit medical products;

Emphasizing 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;

Recalling the WHO global strategy and plan of action on public health, innovation and intellectual property, in particular element three, which calls for establishing and strengthening regulatory capacity in developing countries as one effective policy for building and improving innovative capacity, and element six, which promotes establishing and strengthening mechanisms to improve ethical review and regulate the quality, safety and efficacy of health products and medical devices;

Noting with appreciation the many existing national and regional efforts to strengthen regulatory capacity (including through a variety of models), improve regulatory coherence and convergence among regulatory authorities, and enhance good governance, including transparency in decision-making, leading to the improved availability of quality, safe, efficacious and affordable medical products, such as the European Union regulatory framework for medical products, work under way in PAHO following the adoption by its Directing Council in 2010 of resolution CD50.R9 on strengthening national regulatory authorities for medicines and biologicals, the African Medicines Regulatory Harmonization Initiative, and the regulatory harmonization and cooperation work in ASEAN;

Noting the ongoing collaboration between national and regional regulatory authorities in promoting cooperation among regulatory authorities at the regional and global levels;

Recognizing the significant investments made in the procurement of medicines through national health budgets and global health initiatives;

Also recognizing the essential role of WHO's prequalification programme in facilitating procurement of medical products with assured quality, safety and efficacy;

Stressing that the strengthening of regulatory systems should complement the efforts of the Secretariat and Member States to promote access to affordable medical products with assured quality, safety and efficacy;

Recalling the WHO good clinical practices that focus on the protection of human research subjects;

Recalling also WHO's ongoing reform agenda and welcoming in this regard the establishment in November 2012 of the Health Systems and Innovation cluster,

1. URGES Member States:[4]

(1) to strengthen national regulatory systems, including – as appropriate and voluntarily – by:

(a) undergoing self-evaluations, including with WHO's support, to identify the strengths and opportunities for improvement in regulatory system functions, as a first step towards formulating plans for regulatory system strengthening, including through WHO-coordinated institutional development plans;

[4] And, where applicable, regional economic integration organizations.

(b) collecting data on regulatory system performance to enable analysis and benchmarking for improved systems in the future;

(c) developing strong legal foundations and political leadership to underpin a regulatory system with a clear focus on patient safety and transparency in decision-making;

(d) identifying and developing a core set of regulatory functions to meet country and/or regional needs, such as market control and postmarket surveillance;

(e) developing needed competencies as an integral part of, although not limited to, the health workforce, and encouraging the development of the regulatory field as a profession;

(f) facilitating the use of relevant guidance and science-based outputs of WHO expert committees and good regulatory practices at the national, regional and international levels;

(g) devising and implementing strategies to address the increasing complexities of supply chains;

(2) to engage in global, regional and subregional networks of national regulatory authorities, as appropriate, recognizing the importance of collaboration to pool regulatory capacities to promote greater access to quality, safe, efficacious and affordable medical products;

(3) to promote international cooperation, as appropriate, for collaboration and information sharing, including through electronic platforms;

(4) to support regulatory systems for medical products with appropriate funding as an essential component of the health system;

(5) to support regulatory system strengthening as an essential component of the development or expansion of local or regional production of quality, safe and efficacious medical products;

(6) to achieve access to and rational use of quality, safe, efficacious and affordable essential medicines, noting the growing emergence of resistance, and as a foundation for achieving broader access to quality, safe, efficacious and affordable medical products;

(7) to support WHO's institutional capacity relating to promoting access to and rational use of quality, safe, efficacious and affordable medical products in the context of universal health coverage;

(8) to strengthen the national and regional initiatives of regulatory authorities to improve regulatory capacities for review of medical products, promoting WHO's long-term objective of supporting the strengthening of national regulatory authority capacity among Member States;

(9) to support WHO's prequalification programme, including exploring modalities in consultation with Member States[5] for improved sustainability of this critical programme;

(10) to identify the need to strengthen regulatory system capacity, collaboration and cooperation in the technically complex areas where substantial gaps may still exist, such as the regulation of biotherapeutic products, blood products, and in vitro diagnostics;

2. REQUESTS the Director-General:

(1) to continue to support Member States, upon their request, in the area of regulatory system strengthening, including, as appropriate, by continuing to:

[5] And, where applicable, regional economic integration organizations.

(a) evaluate national regulatory systems;

(b) apply WHO evaluation tools;

(c) generate and analyse evidence of regulatory system performance;

(d) facilitate the formulation and implementation of institutional development plans;

(e) provide technical support to national regulatory authorities and governments;

(2) to continue to develop appropriate norms, standards and guidelines, taking into account national, regional and international needs and initiatives, in accordance with WHO principles;

(3) to ensure that all relevant parts of the Organization, at all levels, are actively engaged and coordinated in the carrying out of WHO's mandate pertaining to regulatory system strengthening as an integrated part of health system development, recognizing that WHO's support in this critical area, particularly for developing countries, may be required, as appropriate, well into the future;

(4) to prioritize support for establishing and strengthening regional and subregional networks of regulatory authorities, as appropriate, including strengthening areas of regulation of health products that are the least developed, such as regulation of medical devices, including diagnostics;

(5) to promote the greater participation of Member States in existing international and regional initiatives for collaboration and cooperation in accordance with WHO principles and guidelines;

(6) to strengthen WHO's prequalification programme, including its integration and coherence, taking into account the needs and capacities of national and regional regulatory systems to assist in ensuring a supply of quality, safe, efficacious and affordable medical products;

(7) to support the building-up of effective national and regional regulatory bodies and networks;

(8) to 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;

(9) to raise awareness of the importance of effective regulatory systems within the health system context;

(10) to increase support and guidance for strengthening the capacity to regulate increasingly complex biological products, with the focus on biotherapeutic products, blood products and associated in vitro diagnostics, and, where appropriate, on new medicines for human use based on gene therapy, somatic-cell therapy and tissue engineering;

(11) to ensure that any activity carried out under this resolution does not duplicate or circumvent the work plan and mandate of the Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medical products;

(12) to report to the Seventieth and Seventy-second World Health Assemblies on progress in the implementation of this resolution.

(Ninth plenary meeting, 24 May 2014 –
Committee B, fourth report)

WHA Resolutions

WHA67.21: Access to biotherapeutic products, including similar biotherapeutic products,[1] and ensuring their quality, safety and efficacy[2]

The Sixty-seventh World Health Assembly,

Having considered the report on regulatory system strengthening;[3]

Recalling the Constitution of the World Health Organization, which affirms that the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition;

Noting with particular concern that for millions of people, the right to the enjoyment of the highest attainable standard of physical and mental health, including access to medicines, remains a distant goal; that especially for children and those living in poverty, the likelihood of achieving this goal is becoming increasingly remote; that millions of people are driven below the poverty line each year because of catastrophic out-of-pocket payments for health care; and that excessive out-of-pocket payments can discourage the impoverished from seeking or continuing care;

Recalling resolution WHA55.14 on ensuring accessibility of essential medicines, which recognizes the responsibility of Member States to support solid scientific evidence, excluding any biased information or external pressures that may be detrimental to public health;

Further recalling that in resolution WHA55.14 the Health Assembly urged Member States, inter alia, to reaffirm their commitment to increasing access to medicines, and to translate such commitment into specific regulation within countries, especially enactment of national drug policies and establishment of lists of essential medicines based on evidence and with reference to WHO's Model List, and into actions designed to promote policy for, access to, and quality and rational use of, medicines within national health systems;

Considering that one of the objectives of pharmaceutical regulation is the assurance of the quality, safety and efficacy of pharmaceutical products through the regulatory processes of authorization, vigilance and monitoring;

Considering also that national pharmaceutical regulation should contribute to the performance and sustainability of health systems and the general welfare of society;

Considering further that an update of the norms and standards applicable to medicines is required in the light of advances made in biotechnology, and the new generation of medicines introduced as a result, in order to ensure the entry into the market of medicines that are affordable, safe, efficacious, of quality and accessible in a timely and adequate fashion;

Recognizing that the use of such medicines has a positive impact on morbidity and mortality rates and that, while there are multiple barriers to access, the high cost of such medicines affects the sustainability of health systems and could in many cases affect access to them;

Noting the importance of, and using as appropriate, WHO's Expert Committee on Biological Standardization's guidelines on evaluation of similar biotherapeutic products (2009), and recognizing the need to update them, particularly in terms of technological advances and characterization, in order to promote more efficient regulatory frameworks from a public health

[1] Acknowledging that national authorities may use different terminologies when referring to similar biotherapeutic products.

[2] See Annex 6 for the financial and administrative implications for the Secretariat of this resolution.

[3] Document A67/32.

perspective that ensure the efficacy, quality and safety of these products at the national and regional levels;

Conscious that similar biotherapeutic products could be more affordable and offer better access to treatments of biological origin, while ensuring quality, safety and efficacy,

1. URGES Member States:[4]

(1) to develop or strengthen, as appropriate, national regulatory assessment and authorization frameworks, with a view to meeting the public health needs for biotherapeutic products, including similar biotherapeutic products;

(2) to develop the necessary scientific expertise to facilitate development of solid, scientifically-based regulatory frameworks that promote access to products that are affordable, safe, efficacious and of quality, taking note of the relevant WHO guidelines that may be adapted to the national context and capacity;

(3) to work to ensure that the introduction of new national regulations, where appropriate, does not constitute a barrier to access to quality, safe, efficacious and affordable biotherapeutic products, including similar biotherapeutic products;

2. REQUESTS the Director-General:

(1) to support Member States in strengthening their capacity in the area of the health regulation of biotherapeutic products, including similar biotherapeutic products;

(2) to support, as appropriate, the development of national regulatory frameworks that promote access to quality, safe, efficacious and affordable biotherapeutic products, including similar biotherapeutic products;

(3) to encourage and promote cooperation and exchange of information, as appropriate, among Member States in relation to biotherapeutic products, including similar biotherapeutic products;

(4) to convene WHO's Expert Committee on Biological Standardization to update the 2009 guidelines, taking into account the technological advances for the characterization of biotherapeutic products and considering national regulatory needs and capacities and to report on the update to the Executive Board;

(5) to report to the Sixty-ninth World Health Assembly on progress in the implementation of this resolution.

(Ninth plenary meeting, 24 May 2014 –
Committee B, fourth report)

[4] And, where applicable, regional economic integration organizations.

Consultation documents

To receive draft monographs by email please contact Mrs Wendy Bonny (bonnyw@who.int), specifying that you wish to be added to the electronic mailing list.

The International Pharmacopoeia

Misoprostolum
Misoprostol

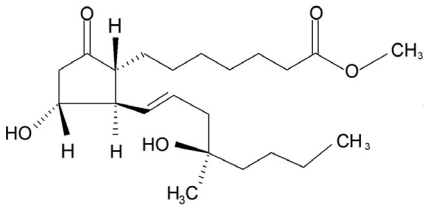
This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.602, January 2015).

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, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.**

Molecular formula. $C_{22}H_{38}O_5$

Relative molecular mass. 382.5

Graphic formula



Chemical name. Mixture of methyl 7-[(1RS, 2RS, 3RS)-3-hydroxy-2-[(1E, 4RS)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl] heptanoate and methyl 7-[(1RS, 2RS, 3RS)-3-hydroxy-2-[(1E, 4SR)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl] heptanoate; CAS Reg. No. 59122-46-2.

Description. Clear, colourless or yellowish, oily liquid.

Solubility. Practically insoluble in water R, soluble in dehydrated ethanol R, sparingly soluble in acetonitrile R.

Category. Prostaglandin (PGE) analogue.

Storage. Misoprostol neat oil should be kept in a tightly sealed container and stored at a temperature between -25 and -10°C.

Additional information. Misoprostol is hygroscopic. It is gradually degraded at room temperature, the degradation being faster at higher temperatures.

Requirements

Definition. Misoprostol contains not less than 96.0% and not more than 102.0% of $C_{22}H_{38}O_5$ with reference to the anhydrous substance.

Identity tests

Either test A 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 misoprostol RS or with the reference spectrum of misoprostol.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R3 as the coating substance and a mixture of 8 volumes of toluene R, 2 volumes of ethyl acetate R, 1 volume of dehydrated ethanol R and 0.1 volume of glacial acetic acid R as the mobile phase, prepared immediately before use. Apply separately to the plate 100 µL of each of the following two solutions in dehydrated ethanol R. For solution (1) use 0.1 mg of the test substance per mL. For solution (2) use 0.1 mg of misoprostol RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air, expose it to the vapour of iodine R and examine the chromatogram in daylight.

   The principal spot obtained with solution (1) corresponds in position, appearance and intensity to that obtained with solution (2).

C. See the test described under "Assay". The retention time of the principal peak in the chromatogram obtained from solution (1) is similar to that in the chromatogram obtained from solution (2).

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, method A, using 1.0 mL of a 10 mg per mL solution of the test substance in methanol R; the water content is not more than 10 mg/g.

Related substances

Prepare fresh solutions and perform the tests without delay.

Carry out the test as described under 1.14.4 High performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with octadecylsilyl silica gel (5 µm).[1]

Use the following conditions for gradient elution:

mobile phase A: mix 28 volumes of acetonitrile R with 69 volumes of water R and 3 volumes of methanol R;

mobile phase B: mix 47 volumes of acetonitrile R with 50 volumes of water R and 3 volumes of methanol R.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0–5	100	0	equilibration
5–15	100 to 65	0 to 35	linear gradient
15–22	65	35	isocratic
22–25	65 to 0	35 to 100	linear gradient
25–30	0	100	isocratic
30–32	0 to 100	100 to 0	linear gradient
32–35	100	0	re-equilibration

[1] An Ascentis Express C18 column was found suitable.

Maintain the column temperature at 35°C.

Prepare the following solutions using a mixture of 31 volumes of acetonitrile R and 69 volumes of water R as solvent. For solution (1) dissolve 50 mg of the test substance in 10 mL and sonicate for about 10 minutes. Ensure that the temperature of the sonication bath is below room temperature to avoid degradation of misoprostol. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 10 µg of misoprostol per mL. For solution (3) heat 5 mL of solution (1) in a water bath at 75°C for 1 hour.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 200 nm. Store the samples at 4°C during analysis using a cooled autosampler.

Inject 20 µL of solution (3). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 5.0, where Hp is the height above the extrapolated baseline of the peak due to impurity A (with a relative retention of about 0.95 with reference to misoprostol (retention time about 21 minutes)) and Hv is the height above the extrapolated baseline at the lowest point of the curve separating the peak due to impurity A from the peak due to misoprostol. Inject alternately 20 µL each of solutions (1) and (2).

In the chromatogram obtained with solution (1) the sum of the areas of peaks eluting with a relative retention between 0.80 and 0.98 with reference to misoprostol is not greater than 7.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%). The area of any other impurity peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%). The sum of the areas of all peaks, other than the principal peak, is not greater than 10 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0%). Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Diastereoisomers

Carry out the test as described under 1.14.4 High performance liquid chromatography using a stainless steel column (15 cm × 2.1 mm) packed with silica gel for chromatography R (3.5 µm).[2] As the mobile phase use a mixture of 4 volumes of 2-propanol R, 96 volumes of heptane R and 0.1 volume of trifluoroacetic acid R.

As the test solution use 1.0 mg of the test substance per mL of a mixture of 4 volumes of 2-propanol R and 96 volumes of heptane R.

Maintain the column temperature at 25°C.

Operate with a flow rate of 0.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 205 nm. Store the samples at 4°C during analysis using a cooled autosampler.

Inject 10 µL of the test solution.

The chromatogram shows two principal peaks due to misoprostol at retention times of about 14 and 16 minutes. The test is not valid unless the resolution between these two peaks is at least 2.0.

Measure the areas of the two peaks corresponding to misoprostol. The first peak of misoprostol is 45% –55% of the sum of the areas of the two peaks due to misoprostol.

[2] An Xbridge HILIC column was found suitable.

Assay

Carry out the test as described under 1.14.4 High performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with octadecylsilyl silica gel (5 µm)[3]. As the mobile phase use a mixture of 45 volumes of acetonitrile R and 55 volumes of water.

Prepare the following solutions in the mobile phase. For solution (1) use 0.1 mg of misoprostol per mL. For solution (2) use 0.1 mg of misoprostol RS per mL.

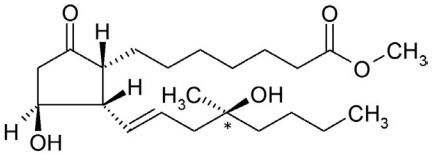
Maintain the column temperature at 35°C.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 200 nm. Store the samples at 4°C during analysis using a cooled autosampler.

Inject alternately 20 µL each of solutions (1) and (2). The test is not valid unless the symmetry factor of the peak due to misoprostol is between 0.8 and 1.5.

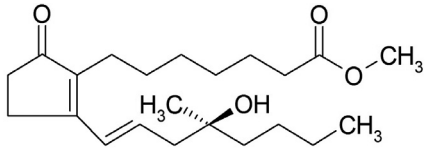
Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of $C_{22}H_{38}O_5$ with reference to the anhydrous substance.

Impurities



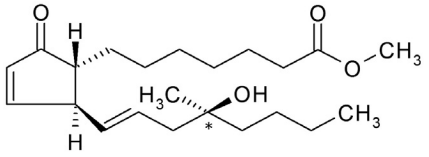
its epimer at C* and their enantiomers

A. *[chemical name to be added]* (8-epimisoprostol)



and enantiomer

D. *[chemical name to be added]* (misoprostol B)



its epimer at C* and their enantiomers

C. *[chemical name to be added]* (misoprostol A)

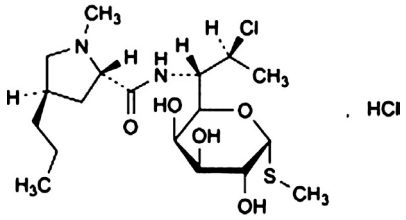
***

[3] An Ascentis Express C18 column was found suitable.

Clindamycini hydrochloridum
Clindamycin hydrochloride

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.603, January 2015).

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, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.**



$C_{18}H_{33}ClN_2O_5S$, HCl

Relative molecular mass. 461.5

Chemical name

Methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-1-methyl-4-propyl-2-pyrrolidinyl]carbonyl]amino]-l-thio-L-*threo*-α-D-galacto-octopyranoside hydrochloride; CAS Reg.No.21462-39-5.

Description. A white or almost white, crystalline powder.

Solubility. Very soluble in water, freely soluble in methanol R, and slightly soluble in ethanol (~750 g/L) TS.

Category. Antibacterial.

Storage. Clindamycin hydrochloride should be kept in a tightly closed container.

Requirements

Definition. Clindamycin hydrochloride contains not less than 91.0% and not more than 102.0% of $C_{18}H_{33}ClN_2O_5S$, HCl, calculated with reference to the anhydrous substance.

Identity test

• Either tests A and E or B, D and E or C, D and E 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 clindamycin hydrochloride RS or with the *reference spectrum* of clindamycin hydrochloride.

B. Carry out the test as described under 1.14.1. Thin layer chromatography using silica gel R1 as the coating substance and the upper layer of a mixture of 19 volumes of 2-propanol R, 38 volumes of a solution of ammonium acetate (~150 g/L) TS adjusted to pH 9.6 with ammonia (~260 g/L) TS and 43 volumes of ethyl acetate R as the mobile phase. Apply separately to the plate 5 µL of each of the following three solutions in methanol R. For solution (A) use 1 mg of test substance per mL. For solution (B) use 1 mg of Clindamycin hydrochloride RS per mL. For solution (C) use 1 mg of Clindamycin hydrochloride

RS and 1 mg of lincomycin hydrochloride RS per mL. After removing the plate from the chromatographic chamber dry the plate in air and spray with potassium permanganate (~1 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). The test is not valid unless the chromatogram obtained with solution (C) shows 2 clearly separated spots.

C. See the test described under "Assay". The principal peak in the chromatogram obtained with solution (1) is similar in retention time to the principal peak in the chromatogram obtained with solution (2).

D. Dissolve about 10 mg in 2 mL of hydrochloric acid (~200 g/L) TS and heat on a water-bath for 3 minutes. Add 3 mL of sodium carbonate (106 g/L) TS and 1 mL of sodium nitroprusside (20 g/L) TS. A violet-red colour develops.

E. A 0.01 g/mL solution yields reaction A described under 2.1 General identification tests as characteristic of chlorides.

Specific optical rotation. Use a 40.0 mg/mL solution and calculate with reference to the anhydrous substance: $[\alpha]_D^{20°C}$ = +135° to +150°.

Sulfated ash. Not more than 5.0 mg/g.

Water. Determine as described under 2.8 Determination of water by Karl Fischer Method, Method A, using 0.5 g of the substance. The water content is not less than 30 mg/g and not more than 60 mg/g.

pH value. pH of a 100 mg/mL solution in carbon-dioxide-free water R, 3.0–5.0.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under "Assay".

Prepare the following solutions in the mobile phase. For solution (1) dissolve 100 mg of the test substance and dilute to 25.0 mL. For solution (2) dilute 2.0 mL of solution (1) to 100.0 mL. For solution (3) dissolve 100 mg of clindamycin hydrochloride RS in a 25 mL volumetric flask.

Inject alternately 20 µL each of solution (1), (2) and (3). Record the chromatograms for about 2 times the retention time of clindamycin (retention time about 10 minutes).

In the chromatogram obtained with solution (3) the peaks are eluted at the following relative retention with reference to clindamycin (retention time about 10 minutes): impurity A (lincomycin) about 0.4; impurity B (clindamycin B) about 0.65; impurity C (7-epiclindamycin) about 0.8. The test is not valid unless the resolutions between the peaks due to impurities B and C and impurity C and clindamycin are at least 3.0.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to either impurity B or impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);
- the area of any other peak, other than the principal peak, is not greater than 0.5 times 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 3 times the area of the principal peak in the chromatogram obtained with solution (2) (6.0%). Disregard any peak with an area less than 0.025 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Assay. 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 particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).[1] As the mobile

[1] Hypersil BDS 5 µm was found to be suitable.

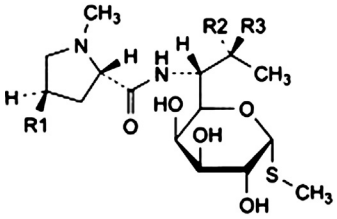
phase use a mixture of 45 volumes of acetonitrile R and 55 volumes of potassium dihydrogen phosphate (6.8 g/L) TS adjusted to pH 7.5 with potassium hydroxide (~400 g/L) TS.

Prepare the following solutions in mobile phase. For solution (1) use a solution containing 1.0 mg of the test substance per mL. For solution (2) use a solution containing 1.0 mg of clindamycin hydrochloride 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 210 nm. Inject alternately 20 µL each of solutions (1) and (2).

Measure the areas of the peaks corresponding to clindamycin obtained in the chromatograms from solution (1) and (2) and calculate the percentage content of clindamycin hydrochloride ($C_{18}H_{33}ClN_2O_5S$, HCl) using the declared content of $C_{18}H_{33}ClN_2O_5S$, HCl in clindamycin hydrochloride RS.

Impurities



A. R1=CH2-CH2-CH3, R2=OH, R3=H: methyl 6,8-dideoxy-6-[[[(2S,4R)- 1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-d-erythro-α-d-galacto-octopyranoside (lincomycin)

B. R1=C2H5, R2=H, R3=Cl: methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)- 4-ethyl-1-methylpyrrolidin-2-yl]carbonyl]amino]-1-thio-l-threo-α-d-galacto-octopyranoside (clindamycin B)

C. R1=CH2-CH2-CH3, R2=Cl, R3=H: methyl 7-chloro-6,7,8-trideoxy-6- [[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-d-erythro-α-d-galacto-octopyranoside (7-epiclindamycin)

Reagents to be established

Hydrochloric acid (~200 g/L) TS
Procedure. Dilute hydrochloric acid (~250 g/L) TS with water to contain approximately 200 g of HCl in 1000 mL (approximately 5.5 mol/L).

Sodium carbonate (106 g/L) TS
A solution of sodium carbonate R containing about 106 g of Na_2CO_3 per litre (approximately 1 mol/L).

Sodium nitroprusside (20 g/L) TS
A solution of sodium nitroprusside R containing about 20 g of $Na_2Fe(NO)(CN)_5$ per litre.
Note: Sodium nitroprusside (20 g/L) TS must be freshly prepared.

Potassium dihydrogen phosphate (6.8 g/L) TS
A solution of potassium dihydrogen phosphate R containing 6.8 g of KH_2PO_4 per litre (0.1 mol/L).

***

Clindamycini hydrochloridi capsulae
Clindamycin hydrochloride capsules

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.604, January 2015).

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, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.**

Category. Antibacterial.

Storage. Clindamycin hydrochloride capsules should be kept in a tightly closed container.

Additional information. Strength in the current WHO Model list of essential medicines (EML): 150 mg (as hydrochloride). Strengths in the current EML for Children: 150 mg (as hydrochloride).

Labelling. The designation on the container should state the quantity of clindamycin hydrochloride in terms of the equivalent amount of clindamycin. 150 mg of clindamycin is approximately equivalent to 162.9 mg of clindamycin hydrochloride.

Requirements

Comply with the monograph for Capsules.

Definition. Clindamycin hydrochloride capsules contain clindamycin hydrochloride. They contain not less than 90.0% and not more than 110.0% of the amount of $C_{18}H_{33}ClN_2O_5S$ stated on the label.

Identity tests

• Either tests A and D or B and D or C and D may be applied.

A. Shake a quantity of the contents of the capsules containing the equivalent of 30 mg of clindamycin with 15 mL of dichlormethane R, filter and evaporate the filtrate to dryness. 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 clindamycin hydrochloride RS, treated in the same way as the test substance, or with the reference spectrum of clindamycin hydrochloride.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R1 as the coating substance and the upper layer of a mixture of 19 volumes of 2-propanol R, 38 volumes of a solution of ammonium acetate (~150 g/L) TS adjusted to pH 9.6 with ammonia (~260 g/L) TS and 43 volumes of ethyl acetate R as the mobile phase. Apply separately to the plate 5 µL of each of the following three solutions. For solution (A) shake a quantity of the contents of the capsules equivalent to 10 mg of Clindamycin with 10 mL of methanol R, filter and use the clear filtrate. For solution (B) use 1 mg of clindamycin hydrochloride RS per mL of methanol R. For solution (C) use 1 mg of clindamycin hydrochloride RS and 1 mg of lincomycin hydrochloride RS per mL of methanol R. After removing the plate from the chromatographic chamber allow it to dry in air and spray with potassium permanganate (~1 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). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

D. See the method 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).

E. Shake a quantity of the contents of the capsules containing 50 mg of Clindamycin with 5 mL of water and filter. The clear filtrate yields the reactions described under 2.1 General identification tests as characteristic of chlorides.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, method A, using a quantity of the contents of the capsules equivalent to 0.5 g of Clindamycin; the water content is not more than 70 mg/g.

Dissolution/Disintegration

Either test A or test B may be applied.

A. **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 water and rotating the paddle at 50 revolutions per minute. At 30 minutes withdraw a sample of 15 mL of the medium from each vessel and filter, discarding the first 10 mL of the filtrate. Prepare standard solution as follows: dissolve a suitable amount of clindamycin hydrochloride RS, then add a suitable volume of the dissolution medium to obtain a concentration of 167 µg per mL. Determine the content of clindamycin ($C_{18}H_{33}ClN_2O_5S$) in the filtrate according to the method below.

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

For each of the capsules tested calculate the amount of clindamycin ($C_{18}H_{33}ClN_2O_5S$) in the medium using the declared content of $C_{18}H_{33}ClN_2O_5S$,HCl in clindamycin hydrochloride RS. Evaluate the results as described under 5.5 Dissolution test for solid oral dosage forms, Acceptance criteria. The amount in solution for each capsule is not less than 80% (Q) of the amount declared on the label.

B. **Disintegration**. Comply with 5.3 Disintegration test for tablets and capsules operating the apparatus for 15 minutes. If the capsules do not comply carry out test A (Dissolution) above.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under "Assay".

Prepare the following solutions in the mobile phase. For solution (1) transfer a quantity of the contents of the capsules equivalent to about 100 mg of Clindamycin into a 25 mL volumetric flask. Add about 20 mL of mobile phase and sonicate for 10 minutes. Dilute to volume with mobile phase, mix and filter. For solution (2) dilute 2.0 mL of solution (1) to 100.0 mL. For solution (3) dissolve 100 mg of clindamycin hydrochloride RS in a 25 mL volumetric flask.

Inject alternately 20 µL each of solutions (1), (2) and (3), Record the chromatograms for 2 times the retention time of clindamycin (retention time about 10 minutes).

In the chromatogram obtained with solution (3) the peaks are eluted at the following relative retention with reference to clindamycin (retention time about 10 minutes): impurity A (lincomycin) about 0.4; impurity B (clindamycin B) about 0.65; impurity C (7-epiclindamycin) about 0.8. The test is not valid unless the resolutions between the peaks due to impurities B and C and impurity C and clindamycin are at least 3.0.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to either impurity B or impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);
- the area of any peak, corresponding to impurity A is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Assay. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25cm × 4.6mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm). [1] As the mobile phase use a mixture of 45 volumes of acetonitrile R and 55 volumes of a 6.8 g/L solution of potassium dihydrogen phosphate R adjusted to pH 7.5 with potassium hydroxide (~400 g/L) TS.

Prepare the following solutions in mobile phase. For solution (1) weigh and mix the contents of 20 capsules. Transfer a quantity of the mixed contents equivalent to about 100 mg of Clindamycin, accurately weighed, into a 100 mL volumetric flask. Add about 80 mL of the mobile phase, sonicate for 10 minutes, make up to volume with the mobile phase, mix and filter. For solution (2) use a solution containing 1.1 mg of Clindamycin hydrochloride 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 210 nm.

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

Measure the areas of the peaks corresponding to clindamycin obtained in the chromatograms from solution (1) and (2) and calculate the percentage content of clindamycin ($C_{18}H_{33}ClN_2O_5S$) in the capsules using the declared content of $C_{18}H_{33}ClN_2O_5S,HCl$ in clindamycin hydrochloride RS. Each mg of $C_{18}H_{33}ClN_2O_5S,HCl$ is equivalent to 0.9209 mg of $C_{18}H_{33}ClN_2O_5S$.

Impurities. The impurities limited by the requirements of this monograph are impurity A, B and C listed in the monograph for Clindamycin hydrochloride.

***

[1] Hypersil BDS 5 µm is suitable.

Dextromethorphani hydrobromidum
Dextromethorphan hydrobromide

This is a draft proposal for The International Pharmacopoeia (Working document QAS/15.605, January 2015).

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.**

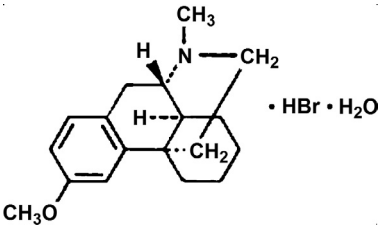
*[**Note from the Secretariat.** It is proposed to revise the monograph on Dextromethorphan hydrobromide.]*

*[**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. $C_{18}H_{25}NO,HBr,H_2O$

Relative molecular mass. 370.3

Graphic formula.



Chemical name.
(+)-3-Methoxy-17-methyl-9α,13α-14α-morphinan hydrobromide monohydrate; (+)-*cis*-1,3,4,9,10,10a-hexahydro-6-methoxy-11-methyl-2*H*-10,4a-iminoethanophenanthrene hydrobromide monohydrate; CAS Reg. No. 6700-34-1 (monohydrate).

Description. A white or almost white, crystalline powder.

Solubility. Sparingly soluble in water; freely soluble in ethanol (~750 g/l) TS; practically insoluble in ether R.

Category. Antitussive.

Storage. Dextromethorphan hydrobromide should be kept in a well-closed container.

Requirements

Definition. Dextromethorphan hydrobromide contains not less than 98.0% and not more than 101.0% of $C_{18}H_{25}NO,HBr$, calculated with reference to the anhydrous substance.

Identity tests

- Either tests A, F and E or tests B, F, G and E may be applied.

A. Dry a small quantity of the test substance for 4 hours under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) over phosphorus pentoxide R and 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 dextromethorphan hydrobromide RS similarly prepared or with the *reference spectrum* of dextromethorphan hydrobromide.

B. The absorption spectrum of a 0.10 mg/ml solution in sodium hydroxide (0.1 mol/l) VS, when observed between 230 nm and 350 nm, exhibits a maximum at 280 nm; the absorbance of a 1 cm layer at this wavelength is about 0.59.

C. *[deleted as part of the proposed revision]*

D. *[deleted as part of the proposed revision]*

E. To a 5 mg/ml solution add 0.25 ml of nitric acid (~130 g/l) TS; this test yields reaction B described under 2.1 General identification tests as characteristic of bromides.

F. Determine the specific optical rotation using a 20 mg/mL solution of the test substance in hydrochloric acid (0.1 mol/L) VS. Calculated with reference to the anhydrous substance; the specific optical rotation is between +28.0° to +30.0°.

G. 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 2 volumes of ammonia (~260 g/L) TS, 10 volumes of dichloromethane R, 13 volumes of methanol R, 20 volumes of ethyl acetate R and 55 volumes of toluene R as the mobile phase. Apply separately to the plate 5 µL of each of the following 2 solutions in methanol R containing (A) 2.5 mg of the test substance per mL and (B) 2.5 mg of dextromethorphan hydrobromide RS per mL. Develop the plate for a distance of about 15 cm. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of air, spray it with potassium iodobismuthate/tartaric acid TS and examine the chromatogram in daylight. The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).

Sulfated ash. Not more than 1.0 mg/g.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using about 0.2 g of the substance; the water content is not less than 35 mg/g and not more than 55 mg/g.

pH value. Dissolve 0.4 g in carbon-dioxide-free water R using gentle heat, dilute to 20 ml with the same solvent and measure the pH at 20°C; the value lies between 5.2 and 6.5.

Dimethylaniline. Dissolve 0.5 g in 15 ml of water using gentle heat, cool and add 4 ml of acetic acid (~60 g/l) TS, 1 ml of sodium nitrite (10 g/l) TS and sufficient water to produce 25 ml. Prepare similarly a reference solution containing 5 µg of N,N-dimethylaniline R in 25 ml. The colour produced in the test solution is not more intense than that produced in the reference solution when compared as described under 1.11 Colour of liquids; the dimethylaniline content is not more than 10 µg/g.

Phenolic substances. To 5 mg add 1 drop of hydrochloric acid (~70 g/l) TS, 1 ml of water and 0.2 ml of ferric chloride (50 g/l) TS. Mix, add 0.2 ml of potassium ferricyanide (50 g/l) TS, dilute to 5 ml with water, shake well and allow to stand for 15 minutes; the solution is yellowish brown and shows no greenish or blue colour.

Levomethorphan. 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 particles of

silica gel, the surface of which has been modified with chemically-bonded cellulose tris(4-methybenzoate) groups (5 µm). As the mobile phase use a mixture of 940 volumes of n-hexane R, 60 volumes of 2-propanol R and 1 volume of diethylamine R.

Operate with a flow rate of 0.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 285 nm. Maintain the column at 30°C.

Prepare the following solutions. For solution (1) transfer about 120 mg of the test substance in a 10.0 mL flask. Add 4 mL 2-propanol R, sonicate for about 5 minutes, allow to cool at room temperature and make up to volume with mobile phase. For solution (2) dilute 5.0 mL of solution (1) to 100.0 mL with mobile phase. Dilute 2.0 mL of this solution to 100.0 mL with mobile phase. Prepare solution (3) as indicated in the leaflet of dextromethorphan for system suitability RS (containing a mixture of dextromethorphan and levomethorphan).

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the two principal peaks due to levomethorphan (retention time about 9 minutes) and due to dextromethorphan (retention time of about 12 minutes) is at least 3.

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

In the chromatogram obtained with solution (1) the area of any peak corresponding to levomethorphan is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1 %).

Related substances. 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 particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).

As the mobile phase use a solution prepared as follows: dissolve 3.11 g of docusate sodium R in a mixture of 400 mL of water R and 600 mL of acetonitrile R, add 0.56 g of ammonium nitrate R and adjust to apparent pH 2.0 with glacial acid R.

Operate with a flow of 1.0 mL/min. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm.

Prepare the following solutions in mobile phase. For solution (1) use a solution containing 1.0 mg of the test substance per mL. For solution (2) dilute 1.0 mL of solution (1) to 200.0 mL. For solution (3) dissolve 2 mg of dextromethorphan impurity A RS in 2 mL of solution (1) and dilute to 25.0 mL.

Inject 20 µL of solution (3). The test is not valid unless the resolution between the peaks due to dextromethorphan (retention time about 22 min) and impurity A (with a relative retention of about 1.1) is at least 1.5.

Inject alternately 20 µL each of solutions (1) and (2). Record the chromatograms for about twice the retention time of dextromethorphan.

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to dextromethorphan (retention time about 22 minutes): impurity B about 0.4; impurity C about 0.8; impurity D about 0.9; and impurity A about 1.1.

In the chromatogram obtained with solution (1):

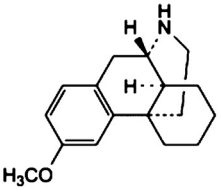
- the area of any peak corresponding to either impurity A, impurity B or impurity D is not greater than the area of the principal peak obtained with solution (2) (0.5 %);

- the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.2, is not greater than the area of the principal peak obtained with solution (2) (0.5%);
- the area or the corrected area of not more than one peak corresponding to either impurity A, impurity B, impurity C or impurity D is greater than 0.5 times the area of the principal peak obtained with solution (2) (0.25 %);
- the area of any other peak, other than the principal peak, is not greater than 0.2 times the area of the principal peak obtained with solution (2) (0.10 %);
- the sum of the corrected area of any peak corresponding to impurity C and the areas of all other peaks, other than the principal peak, is not greater than twice the area of the principal peak obtained with the 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) (0.05%).

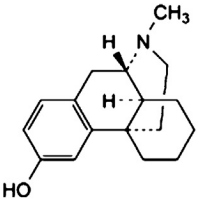
Assay

Dissolve about 0.3 g, accurately weighed, in a mixture of 5.0 mL of hydrochloric acid (0.1 mol/L) VS and 20 mL of dehydrated ethanol R. Titrate with sodium hydroxide (0.1 mol/L) VS, determining the end-point potentiometrically. Read the volume added between the 2 points of inflexion. Each mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 35.23 mg of $C_{18}H_{25}NO,HBr$.

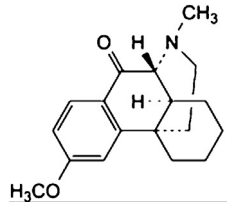
Impurities



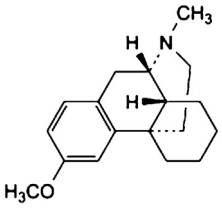
A. *ent*-3-methoxymorphinan,



B. *ent*-17-methylmorphinan-3-ol,



C. *ent*-3-methoxy-17-methylmorphinan-10-one,



D. *ent*-(14S)-3-methoxy-17-methylmorphinan.

Reagents to be established

Potassium iodobismuthate/tartaric acid TS

Stock solution. Suspend 1.7 g of bismuth subnitrate R and 20 g of tartaric acid R in 40 mL of water R. To the suspension add 40 mL of potassium iodide (400 g/L) TS and stir for 1 hour. Filter. The solution may be kept for several days in brown bottles.

Spray solution. Mix immediately before use 5 mL of the stock solution with 15 mL of water R.

Docusate sodium R

Sodium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate.

A commercially available reagent of suitable grade.

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