WHO Drug Information

Contents

ICDRA
547 17th International Conference of Drug Regulatory Authorities

Regulatory collaboration
558 Collaboration, not competition: developing new reliance models

Medicines regulation
567 Comparison of medicines legislation in the East African Community

Safety news
577 Safety warnings
   DPP-4 inhibitors • Polaprezinc • Brimonidine gel • Levonordestrel emergency contraceptives • Direct-acting antivirals • HIV treatment-boosting agents and steroids • Nivolumab • Eculizumab • Anaesthetics and sedatives in young children and pregnant women

580 Known risks
   Pioglitazone • Warfarin and miconazole • Statins • Daptomycin • NSAIDs • Paracetamol • Lurasidone and certain ARVs

581 Labelling changes
   Metformin • Etoricoxib

582 Improved dosing instructions
   Levetiracetam oral solution

583 Unchanged recommendations
   Urine- and plasma-derived medicines

583 Non-compliance with good practices
   Pharmaceuticals International Inc., U.S.

583 Safety reviews started

Regulatory news
584 Pre-market assessment
   EMA publishes clinical reports

584 Post-market surveillance
   Social media campaign on reporting of medicines side effects • EU project to strengthen market surveillance for medical devices • EU–U.S. collaboration on medicines for rare diseases • Japan joins international collaboration on GMP inspections • Mapping of global medicines regulatory initiatives • MHRA and Swissmedic sign agreement

586 Use of medicines
   Report on sales of veterinary antibiotics in Europe • Indian FDC ban reversed

586 Under discussion

   Approved

587 Obeticholic acid • Insulin aspart • Insulin glargine/lixisenatide • Lonotocog alfa • Etelcalcetide • Tenofovir alafenamide • Olaratumab • Palbociclib • Eteplirsen • Baricitinib • Naloxone nasal spray • Edotrotide

589 Biosimilars
   Insulin glargine • Teriparatide • Rituximab • Adalimumab-atto

590 Extension of indications
   Empagliflozin • Maraviroc • Nivolumab • Canakinumab

Publications and events

591 Research and ethics
   Revised CIOMS ethical guidelines

591 Access to medicines
   UN High Level Panel report on access to health technologies • Report of the Lancet Commission on Essential Medicines • Access to Medicine Index 2016 • High price of hepatitis C treatment • Medicines patent and licences database upgraded • Updated paediatric ARV formulary and list

594 Quality of medicines
   Sample testing survey on medicines for women and children • Fighting poor-quality medicines in low- and middle-income countries

595 Antimicrobial resistance
   Landmark UN declaration on antimicrobial resistance • The economic threat of drug-resistant infections

596 Clinical use of medicines
   Mentoring programme

596 Disease updates
   Tuberculosis • Measles • Malaria • Zika

Continued
598 WHO matters

Model prequalification dossier • New medicines invited for prequalification • Seminar for laboratories held in China • “Green” procurement of health commodities • New prequalification fee structure

599 Upcoming events

2017 joint UNICEF-UNFPA-WHO manufacturers meeting

ATC/DDD classification

600 ATC/DDD classification (temporary)
603 ATC/DDD classification (final)

International Nonproprietary Names (INN)

605 Proposed INN: List 116

Abbreviations and websites

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 Pharmaceuticals 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 (freely available at www.who.int/medicines/publications/druginformation) has direct clickable hyperlinks to the documents and web pages referenced.
ICDRA

17th International Conference of Drug Regulatory Authorities

“Patients are waiting: How regulators collectively make a difference”
Present challenges and opportunities - roadmap for the future

The 17th International Conference of Drug Regulatory Authorities (ICDRA) was held in Cape Town, South Africa, on 29 November–2 December 2016. The event was co-hosted by the Medicines Control Council (MCC) of South Africa and WHO.

More than 360 delegates from regulatory authorities of WHO Member States participated in the 17th ICDRA. The recommendations as presented at the end of the conference are set out on the following pages. They are reproduced here as provided by the moderators in the closing plenary session. Feedback, particularly from non-participating authorities, is welcome.

Several common cross-cutting themes emerged from the discussions. These can be further grouped and consolidated and include e.g. improving coordination, reliance, work-sharing and use of regional networks; promoting greater transparency, awareness and communication; enabling preparedness to facilitate crisis management; development of international standards; and provision of technical assistance to support implementation.

WHO intends to develop a further more concise iteration of these recommendations in the form of a work plan, integrating any feedback received and ensuring greater alignment and consistency across the various work streams. This work plan will be prepared later in 2017, and the outcomes of the deliverables will be presented to the 18th ICDRA in September 2018.

WHO will also conduct a general survey seeking feedback on the 17th ICDRA to help inform the structure and content of the next ICDRA. More information on this survey will be published in the next issue of WHO Drug Information.

► Please send your feedback on the 17th ICDRA recommendations to: druginfo@who.int
## 17th ICDRA sessions: Recommendations

<table>
<thead>
<tr>
<th>THEME: Regulatory systems strengthening</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plenary 3</td>
<td>Strengthening of regulatory systems: Follow-up on WHA Resolution 67.20</td>
</tr>
<tr>
<td>Plenary 5</td>
<td>Good regulatory practices: Why are they important?</td>
</tr>
<tr>
<td>Plenary 7</td>
<td>Global scenery of regulatory convergence initiatives: linking opportunities</td>
</tr>
<tr>
<td>Workshop B</td>
<td>Model regulatory framework for medical devices: how to take steps for successful implementation</td>
</tr>
<tr>
<td>Workshop C</td>
<td>Harmonization and work-sharing in pharmacovigilance: What does this mean in practice?</td>
</tr>
<tr>
<td><strong>THEME: Public health emergencies</strong></td>
<td>551</td>
</tr>
<tr>
<td>Plenary 4</td>
<td>Regulatory preparedness for public health emergencies</td>
</tr>
<tr>
<td>Workshop I</td>
<td>Regulators’ response to shortages of supplies</td>
</tr>
<tr>
<td>Workshop J</td>
<td>Regulators’ role in addressing antimicrobial resistance</td>
</tr>
<tr>
<td><strong>THEME: Biologicals</strong></td>
<td>553</td>
</tr>
<tr>
<td>Workshop A</td>
<td>Similar biotherapeutic products</td>
</tr>
<tr>
<td>Workshop D</td>
<td>Blood products – old and new challenges</td>
</tr>
<tr>
<td>Workshop G</td>
<td>Update on vaccines regulation</td>
</tr>
<tr>
<td><strong>THEME: Substandard and falsified medical products</strong></td>
<td>555</td>
</tr>
<tr>
<td>Plenary 6</td>
<td>SSFFC medical products and supply chain integrity</td>
</tr>
<tr>
<td>Workshop F</td>
<td>Effective communications for preventing, detecting and responding to SSFFC medical products</td>
</tr>
<tr>
<td><strong>THEME: Special topics</strong></td>
<td>556</td>
</tr>
<tr>
<td>Workshop E</td>
<td>Regulatory challenges of medical products for maternal &amp; child health</td>
</tr>
<tr>
<td>Workshop H</td>
<td>Safety of herbal medicines: present challenges and opportunities</td>
</tr>
</tbody>
</table>

17th ICDRA website: [www.icdra.co.za](http://www.icdra.co.za)

Information on past ICDRA conferences is available at:
THEME: Regulatory systems strengthening

Plenary 3:
Strengthening of regulatory systems:
Follow-up on WHA Resolution 67.20

Recommendations to WHO
1. Implement a unified policy and harmonized global benchmarking tool, applicable for all medical products; streamline processes where possible to increase efficiency of benchmarking and capacity building.
2. Incorporate an innovative and more coordinated approach to regulatory systems strengthening such as coalition of interested partners and centres of excellence.
3. Promote the concept of reliance, where appropriate, and collaborative decision-making at regional level.
4. Increase transparency in the outcome of benchmarking activities, thereby facilitating reliance.
5. Consider moving away from using the term “Stringent national regulatory authority”.

Recommendations to Member States
1. Work towards attaining at least minimal capacity (functionality) of “regulatory systems”, which includes the concept of reliance and collaborative decision-making.
2. Encourage best use of existing networks for capacity building – e.g., the African Vaccines Regulatory Forum (AVAREF), the Developing Country Vaccine Regulators’ Network (DCVRN), the Pan American Network for Drug Regulatory Harmonization (PANDRH) – to foster collaboration in regulatory activities, including work-sharing.
3. Invest in human resources with the goal of achieving more systemic and predictable outputs from assessors and promote documentation of training and maintaining competency records.

Plenary 5:
Good regulatory practices

Recommendations to WHO
1. Develop a training curriculum for promotion and implementation of the WHO Good regulatory practices (GRP) guideline for all layers of regulatory bodies (supranational, national and subnational levels).
2. Incorporate the use of information technology (websites, mobile applications, etc.) and emphasize staff competency and training as enablers for promoting and implementing GRP.

Recommendations to Member States
1. Concerned bodies including parliamentarians, policy makers and regulators (supranational, national and subnational levels) to be informed/educated on aspects of good regulatory practices.
2. National/subnational levels of regulatory authorities to harmonize legal frameworks and implementation of GRP, requiring both sufficient and competent human resources.
Plenary 7:
Global scenery of regulatory convergence initiatives: linking opportunities

**Recommendations to WHO**
1. Encourage communication and information/work-sharing across existing initiatives in order to optimize their outputs.
2. Explore opportunities to identify technical platforms that would facilitate interactions and acquisition of existing knowledge.
3. Leverage all opportunities for collaboration and de-duplication of work.
4. Start working on indicators of medicinal products’ regulation systems in order to capture progress made in the area of access to medicines.

**Recommendations to Member States**
1. Prioritize initiatives regarding different areas of regulations that will result in facilitating access to medicines for patients.
2. Focus on appropriate resourcing models in order to build a regulatory system that is fit for purpose.
3. Look for opportunities to obtain technical support and capacity building across existing initiatives and networks.
4. Take into full consideration the existing technical standards, while respecting national realities and contexts.

Workshop B:
Model regulatory framework for medical devices: how to take steps for successful implementation

**Recommendations to WHO**
1. Create a technical working group on medical devices.

**Recommendations to Member States**
1. Between 2016-2018, ten Member States implement the basic level of regulatory control as set in the WHO Global Model Regulatory Framework in their national regulatory system.
2. Strengthen regulation capacity of regulators on medical devices, both in countries that do have regulation in place as well as countries that start regulating.

**Ideas from the pre-ICDRA workshop**
*Regulating medical devices: the involvement of stakeholders*
Implementing regulation is more effective and efficient if regulators and stakeholders interact in a timely and interactive manner. Patients would want a plan with clear steps to have safe and accessible medical devices.
Workshop C:  
Harmonization and work-sharing in pharmacovigilance

Recommendations
1. Take stock of work-sharing solutions from established cooperation initiatives (like EU) or bilateral agreements (like ARFA and ANVISA/Infarmed) and strengthen and maintain a pharmacovigilance system based on clear and transparent rules, engagement of all stakeholders and coordinated by an established platform such as WHO.
2. Promote and take advantage of emerging opportunities and harmonization frameworks (such as the African Medicines Regulatory Harmonization African Medicines Regulatory Harmonization, AMRH) including common standards, definitions, instruments and channels of communication.
3. Pharmacovigilance systems should be able to act locally, addressing appropriately any emerging safety concerns.
4. Avoid duplication, in particular share information and existing assessments on signals and safety issues in a timely manner.
5. Consider integrating vigilance systems across different types of products including medical devices and cosmetics.
6. Maintain and further improve centralized system of signal detection, providing a tailored service to Member States on their specific requests.
7. Strengthen collaboration with existing centralized systems/databases (e.g. Eudravigilance and WHO’s global Individual Case Safety Reports database, Vigibase), in order to avoid duplication.
8. Support an integrated pharmacovigilance strategy that engages key stakeholders in an open, transparent and collaborative way to strengthen systems, avoids duplication of efforts and promotes effective use of the limited resources.

THEME:  Public health emergencies

Plenary 4:  
Regulatory preparedness for public health emergencies

Recommendations to WHO
1. Consider the formation of a special WHO led task force on medicine regulation that can be deployed during a public health crisis to provide advice to countries on issues that may arise.
2. Ensure that regulatory support is a priority area of activity as the R&D Blueprint for emerging infectious diseases is implemented.
3. Consult on the needs for further development of the Emergency Use Approval and Listing mechanisms established through the Prequalification programme.
4. Develop guidance, and appropriate forums for dialogue, for developed and developing country regulators, on regulatory pathways, platform technologies and novel clinical trial designs for products against emerging infectious disease pathogens, ensuring that the guidance includes more vulnerable populations such as pregnant women and children.
5. Report back at the 18th ICDRA on progress made on regulatory preparedness for public health emergencies and the integration of this activity into NRA systems strengthening.
Recommendations to Member States
1. Preparedness for public health emergencies is key, so all NRAs should ensure they proactively participate in national preparedness planning processes.
2. Regulators should help drive product development for public health emergencies, not only for diagnostics, vaccines and therapeutics but also for relevant infection control products.
3. Crisis communications are particularly challenging and NRAs need to proactively develop a general communication plan that would include crises, and to develop their capacity, overall, to communicate more effectively.

Workshop I:
Regulatory responses to shortages of supplies

Recommendations to Member States
1. Regulators should encourage and enable the authorization of alternative active pharmaceutical ingredient (API) sources, manufacturing processes and sites for all medicines identified as vulnerable or critical.
2. Governments/regulators should consider shortage reporting systems which feed to national, to regional and to global systems.
3. Governments/regulators should consider the process for special access (including donations) to meet the particular needs of patients.

Workshop J:
Regulatory role in addressing anti-microbial resistance

Recommendations to WHO
1. Continue to support countries on monitoring antimicrobial consumption and use in human and animals. Increase the systems of gathering data on antimicrobial resistance in the health care setting.
2. Continue supporting countries in strengthening their regulatory systems to ensure that the quality of antibiotics/antimicrobials can be assured.

Recommendations to Member States
1. Regulators should consider ways that will facilitate the development of new antibiotics such as harmonized technical standards, scientific advice, accelerated pathways and incentivized research.
2. Member States/regulators should promote the rational use and prescribing of medicines. Actions can include: prohibiting the dispensing of medicines without a prescription, information campaigns, requirements for proper diagnostics, considering the indications for which medicines are indicated.
THEME: Biologicals

Workshop A:
Similar biotherapeutic products

Recommendations to WHO
1. Expand support to Member States in implementing guiding principles for regulatory evaluation of biotherapeutics, including biosimilars, for example to Russian-speaking countries and low- and middle-income countries.
2. Foster collaboration and use of existing regulatory networks to promote information and work-sharing among regulators and provide technical support to enable regulatory evaluation on the basis of up-to-date scientific principles and evidence.
3. Further development, and communication about use, of public standards should be prioritized to help assure quality of biotherapeutics including biosimilars.
4. Provide technical assistance and guidance for regulatory oversight of biosimilars developed through technology transfer.
5. Develop mechanisms to assist countries in linking regulation with guidance on the appropriate use of similar biotherapeutic products.

Recommendations to Member States
1. Given the number of available guidelines for biosimilars (e.g., WHO, EMA, national guidance), the focus should be on the implementation of the existing guidelines.
2. Collaboration is the key for overcoming lack of expertise and experience in many NRAs. For that purpose, better use of existing resources through the networks (e.g., AVAREF and Zazibona in the African region and other relevant networks in other regions) is the way forward.
3. Training as part of long term strategy for building capacity should be accelerated and all relevant training opportunities should be used. For example, the European Network Training Center will soon become available to non-EU regulators.
4. Regulators should provide relevant and useful information to enable health care providers to prescribe and patients to use biosimilars with confidence.

Workshop D:
Blood products – old and new challenges

Recommendations to Member States
1. Member States are encouraged to implement regulation of blood and blood components for transfusion as essential medicines covering all steps “from vein to vein and back” based on current WHO Guidelines including “Good Preparation Practices (GPP)” analogous to pharmaceutical good manufacturing practices and to assure availability and quality of plasma suitable for use in fractionation.
2. Member States are encouraged to implement regulation of reagents and devices essential to the preparation of blood and blood components (e.g., anticoagulant solutions, donor screening assays, compatibility tests, etc.).
3. Member States are encouraged to model new blood regulations on those already established in other countries and to seek
any necessary assistance from such countries and from WHO.

4. Member States are encouraged to regulate snake antivenoms as biological products and to assess the quality, effectiveness and specificity of these products in the context of the country’s specific needs, making use of tools available from WHO including the revised *WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins* and the updated WHO database on snake species and antivenoms.

**Recommendations to WHO**

1. WHO, at the request of Member States, should continue to provide assistance for assessments of national blood regulatory systems.

2. WHO, at the request of Member States, should offer specific training for inspectors and assessors in the regulation of blood and blood components and related reagents and devices, including a focus on strengthening of regional networks.

3. WHO should regularly update the global data base on snake species and antivenoms.

4. WHO, at the request of Member States, should assist in the development of regional reference standards for venoms.

5. WHO should take steps towards eventual inclusion of snake antivenoms in its prequalification programme. The current assessment programme should be continued, with consideration of expansion of support for NRA inspections, critical laboratory testing and promotion of quality-assured manufacturing.

---

**Workshop G:**

**Vaccine regulation**

**Recommendations to WHO**

1. Assist Member States to build capacity at the regional level (e.g., regional blocks and networks) for regulation of vaccine

2. Assist Member States that will transition from vaccine procurement through GAVI to self-procurement of vaccines to prepare adequately and in a timely way for the change.

3. Assist Member States to build pharmacovigilance capacity for vaccine

4. Consider removal of the innocuity test as a requirement for lot release from WHO vaccine guidelines but encourage maintenance of some capacity to perform this test, if needed.

5. Establish a global network of national vaccine control laboratories involved in testing of WHO-prequalified vaccines

**Recommendations to Member States**

1. Consider using regional level approaches (e.g., regional blocks and networks) for regulation of vaccines

2. For efficient lot release testing of vaccines, consider a risk-based approach or networking (reliance) approach

3. Utilize opportunities through WHO, and links with international regulatory platforms (e.g., PAHO, ASEAN, AVAREF and DCVRN), to build capacity for vaccine regulation.
THEME: Substandard and falsified medical products

Formerly known as substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medical products

Plenary 6:
SSFFC medical products and supply chain integrity

Recommendations to WHO
1. WHO is urged to continue regulatory strengthening, with particular emphasis on training in relation to all aspects of the prevention, detection and response to substandard and falsified medical products.
2. WHO is urged to publish data on the scope, scale and harm caused by substandard and falsified medical products.
3. WHO is urged to examine all available and emerging technologies to assist in the tracking, tracing and authentication of medical products, and where necessary screening, testing and reporting of substandard and falsified medical products.

Recommendations to Member States
1. Heads of regulatory agencies are encouraged to raise awareness amongst policy and decision makers, relevant stakeholders and most importantly civil society of the threat posed by substandard and falsified medical products.
2. Member States and regulatory authorities are encouraged to set and implement national/regional strategies to prevent, detect and respond to substandard and falsified medical products, embedded within core regulatory functions.
3. Member States are requested to nominate regulatory technical experts to participate in the WHO Member State Mechanism, and specifically national regulatory focal points to engage with the WHO Global surveillance and monitoring system for substandard and falsified medical products.

Workshop F:
Effective communications – SSFFC

Recommendations to WHO
1. WHO is encouraged to provide best practice communications guidance to Member States, including templates and models for communication, education and awareness campaigns.
2. WHO is encouraged to provide guidance on communication strategies specifically in relation to reacting to substandard and falsified medical products discovered in the supply chain.
3. WHO is encouraged to provide a central communications hub with access available to communications experts in Member States which will house all the advice, knowledge and experience gained from the communications programme developed by WHO.
Recommendations to Member States

1. Member States are encouraged to play an active role in the Communications Working Group of the WHO Member State Mechanism to ensure the proposals developed reflect the needs of all countries.
2. Member States are encouraged to share examples of communication campaigns implemented in their countries to the Member State Mechanism, to improve the knowledge base of communications activities globally, and to enable this experience and learning to be shared with other Member States.
3. Member States are encouraged to deliver national communication and awareness campaigns, offering accurate information, sound advice and reassurance to relevant stakeholders specifically civil society and the young.

THEME: Special topics

Workshop E:
Regulatory challenges of medical products for maternal and child health

Recommendations to Member States

For maternal immunization
Maternal immunization is a field of growing importance to reduce neonatal, infant and maternal mortality, and new vaccines are in development for Group B Streptococcus (GBS) and respiratory syncytial virus (RSV).
1. Implementation of recently developed WHO guidelines on influenza vaccine labelling was recognized as an important step towards wider immunization of pregnant women, and women during the lactation period, with inactivated influenza vaccines.
2. Collection and review of safety data from post-marketing surveillance and post-licensure studies of existing vaccines would contribute to better understanding of the safety in the field.
3. For new vaccines to be used for maternal immunization, randomized, controlled designs with pre-specified clinical and immunological outcomes are the gold standard, with consideration in the trial design of correlates of protection.
4. All national regulatory authorities should review their current language in package inserts/labelling to accurately reflect data while avoiding misleading statements.

For paediatric medicines
1. Member States are still facing challenges to get optimal formulations for children, and there is a need to incentivize research and licensure of paediatric formulations.
2. It is good to see an increase of the number of ongoing studies and registration, but problems still exist in treating children in countries. Every effort should be made to define regulatory requirements for involvement of children in clinical trials.
3. Member States should consider putting in place post-marketing surveillance and pharmacovigilance when new paediatric formulations are introduced.

Recommendations to WHO
1. WHO guidelines on quality, safety and efficacy of RSV vaccines: standardization
and coordination in reaching consensus on that matter is critical.
2. Guidelines for paediatric medicines used in emergency situations (such as the Ebola outbreak) should be developed.
3. There is a need for a clear definition of a child and an adolescent, and consideration of what this means for clinical trials and licensure (particularly important for medicines used in oncology).
4. Registry practices need to be standardized. Good practices for registries need to be developed by WHO.
5. Regulation of paediatric medicines should be a permanent theme for ICDRA.

Workshop H:
Safety of herbal medicines

Recommendations to Member States
1. Member States are encouraged to adopt and subsequently monitor the implementation of existing WHO guidelines pertaining to herbal medicines, according to national circumstances, to define/determine the scope of the effective regulation and safety monitoring of herbal medicines.
2. Member States are encouraged to identify and develop tools to implement appropriate communication strategies aimed at consumers, health care providers, manufacturers and distributors of herbal medicines, in order to facilitate them to make informed decision/choice in their use and clinical application.
3. Member State are encouraged to share good practices in setting key objectives, and/or action taken to overcome safety concerns of herbal medicines, among Member States.

Recommendations to WHO
1. WHO should further coordinate and support Member States in order to strengthen and facilitate collaboration and communication among national regulatory authorities in the area of herbal medicines, especially in sharing information on safety of herbal medicines and on public awareness campaigns relating to herbal medicines, through relevant mechanisms, such as the International Regulatory Cooperation for Herbal Medicines.
2. In order to strengthen the national capacity at the regulatory authorities in conducting comprehensive effective regulation of herbal medicines, WHO should:
   a) identify and coordinate with possible partners to provide tailored capacity-building opportunities to the concerned regulatory authorities;
   b) support exchange among Member States of technical expertise and technical resources that are required in the assessment of herbal medicines for inclusion in the national registration; and
   c) further support Member States in developing methodologies in setting required national standards and reference sources (such as pharmacopoeia) taking into account particulars of herbal medicines, in order to enhance mutual reliance basis for convergence of standards among Member States.
Regulatory collaboration

Collaboration, not competition: developing new reliance models

Exchange of assessment reports (ARs) with regulators outside the European Union (EU)

At a time when modern medicines manufacture and distribution are increasingly globalized, cooperation between medicine regulators has become essential, and multiple models of regulatory collaboration are being implemented in all regions of the world. The European regulatory system for medicines is unique in the global regulatory environment and may serve as a model for other countries or regions for building trust and mutual reliance. The EU Medicines Agencies Network Strategy to 2020 highlights the strong international role that the EU network can play in promoting reliance and work-sharing with other regulators.

This paper provides a discussion of the programmes and initiatives in which medicines regulators rely on collaboration and on assessment work carried out by other regulators while retaining responsibility for their own regulatory decisions. It also proposes some tools and suggestions to make these approaches more systematic. The paper concentrates on assessment of applications for marketing authorization, but many concepts expressed here can be applied to other regulatory areas such as inspections and pharmacovigilance.

Although the focus is on exchange of documents produced by the European Medicines Agency (EMA) and other agencies in the EU network with regulators outside the EU, it is recognized that the EU regulatory system also has much to gain by exchanging experience with, and receiving information from, regulators in other regions of the world.

1 The 28 EU Member States plus Iceland, Liechtenstein and Norway form the European Economic Area (EEA). Most of the EU rules, procedures and practices described in this article apply to all the EEA countries.

Authors:
Riccardo Luigetti, European Medicines Agency (EMA)
Peter Bachmann, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Germany, and Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh)
Emer Cooke, European Medicines Agency (EMA); since 15 November 2016: Department of Essential Medicines and Health Products (EMP), World Health Organization
Tomas Salmonson, Läkemedelsverket (MPA), Sweden, and EMA Committee for Medicinal Products for Human Use (CHMP)

Any feedback on ways to achieve or improve cooperation would be very much appreciated by the EMA and the other agencies in the EU network, and can be addressed to EMA through the mailbox: emainternational@ema.europa.eu.
Introduction

Current regulatory challenges
Modern medicines manufacture and distribution are becoming more and more globalized. As a consequence the manufacturing processes and supply chains of pharmaceutical products, including generics, are increasingly complex. The same medicinal product is often distributed in several countries or world regions and used by patients all over the world. It is also common that different manufacturing phases for the same product take place in different countries, often very far away from each other. At the same time more and more common elements are present in the dossiers submitted in different jurisdictions.

In addition, new medicines coming to the market are often complex products such as biotechnology, gene therapy or cell therapy products, or have sophisticated formulations involving e.g. micellar systems or nanoparticles. Some regulators may lack the resources or specific competences to carry out assessments of these products before they are put on their markets.

In this environment, collaboration among regulators is essential to avoid duplication of work, release scarce resources for more critical areas and speed up patients access to new and/or affordable products.

New models of cooperation
The growing awareness of the need for regulators to work together has led to the emergence of new models of cooperation. The European medicines system is probably the best-established example of regulatory cooperation between medicines authorities, with a legal basis dating from 1965. It has a long history of developing effective cooperation within Europe and may serve as a model for other countries or regions for building trust and mutual reliance. The EU Medicines Agencies Network Strategy to 2020 (1), published in December 2015, highlights collaboration in the global regulatory environment as a strategic priority area and aims at further developing a strong international role for the network by, among other things, capacity building and promoting reliance and work-sharing with other regulators.

A number of other countries and regions have also developed or are developing formal and informal frameworks for cooperation and work-sharing, helping avoid duplication and use resources efficiently. A few examples are given below; the list is far from being exhaustive.

In the Region of the Americas, which comprises 55 countries, the Pan American Network for Drug Regulatory Harmonization (PANDRH) is a forum of national medicine regulatory agencies whose aim is to promote regulatory harmonization between them, including technical guidelines and regulatory processes, while the Caribbean Community (CARICOM) is advancing a project to develop a regional regulatory system.

In Africa, several regional communities and projects are in place to develop cooperation mechanisms, such as the East African Community (EAC) and the Southern African Development Community (SADC), which are working towards harmonization among the participating authorities, and the ZaZiBoNa project, which connects the regulatory systems of the four participating countries (Zambia, Zimbabwe, Botswana and Namibia) with a view to expanding the project to other countries. The African
Vaccine Regulatory Forum (AVAREF) is developing mechanisms and pathways for expedited regulatory review of clinical trials for products being developed to address public health emergencies and neglected diseases, including joint review by regulators and ethics committees. A timeline for the establishment of an African Medicines Agency has been recently established (2).

The Association of Southeast Asian Nations (ASEAN), the Asia-Pacific Economic Cooperation (APEC) and the Gulf Central Committee for Drug Registration (GCC-DR) are among the regional initiatives in Asia working towards harmonization for medicinal products.

Collaboration and reliance
Regulatory collaboration can be achieved in a variety of ways, including information and/or work-sharing and mutual recognition of assessment and inspection results.

Forms of cooperation such as mutual recognition agreements, which require establishment of a strong legal framework, are desirable and should be implemented whenever possible. However, they take a long time to set up, as the regulatory systems involved need to be mutually assessed and shown to be equivalent before implementation.

An alternative way to achieve cooperation and avoid duplication of work is what is often referred to as reliance. Reliance is a broad concept and can be achieved in real life in different ways. In general, reliance implies that the work done is shared by the trusted authority (e.g. through assessment or inspection reports), while the receiving authority uses this work according to its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities. For example when an assessment report for a medicine authorized in the EU is shared with a regulatory authority in Africa, the receiving authority might still need to consider differences in conditions of use, patient population and other parameters. In many cases reliance on the assessment or inspection work carried out by another trusted regulatory authority can be the best way to cooperate effectively. Reliance can be unilateral, bilateral (mutual) or multilateral.

EU registration pathways
The EU regulatory model has evolved significantly over time, particularly since the creation of the European Medicines Agency (EMA), the Centralised Procedure and the Mutual Recognition Procedure in 1995. The various routes to medicines approval in the EU system (Table 1) are

<table>
<thead>
<tr>
<th>Centralised Procedure (CP)</th>
<th>Assessment via EMA, resulting in a single marketing authorization throughout the EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decentralised Procedure (DCP)</td>
<td>Assessment of a new (not previously authorized) medicine by a Reference Member State on behalf of a group of other Member States</td>
</tr>
<tr>
<td>Mutual Recognition Procedure (MRP)</td>
<td>Assessment of a medicine authorized in at least one Member State by a Reference Member State on behalf of a group of other Member States</td>
</tr>
<tr>
<td>National procedures</td>
<td>Assessment by a Member State of a medicine for approval in its own jurisdiction</td>
</tr>
</tbody>
</table>

based on a single assessment system so that any assessment report (AR) from any of the agencies in the EU network can be used as a basis for reliance by other regulators.

Exchange of complete, unredacted ARs plays an important role in regulatory cooperation. EU regulators share their unredacted ARs with regulators outside the EU in several established initiatives and other contexts, as described below. This exchange is often based on confidentiality agreements, but in the spirit of regulatory collaboration ARs can also be exchanged where there is no such agreement in place and the applicant for marketing authorization consents to this sharing. This allows the extensive assessment work carried out by EU experts to be used by other international regulators for the benefit of patients. The different means used to achieve such sharing of ARs in practice are explained later in this paper.

Information-sharing initiatives involving EU ARs

IGDRP information-sharing pilots with EU’s Decentralised and Centralised Procedures

The information-sharing pilot of the International Generic Drug Regulators Programme (IGDRP) was launched in July 2014 using the EU Decentralised Procedure (DCP) as a model for cooperation. It provides a mechanism for sharing of information during the scientific assessment phases of the procedure. During Decentralised Procedures for generics participating in the pilot, ARs are shared by the EU agencies in real time with the participating non-EU authorities, upon request from the company applying for marketing authorization. The receiving authorities benefit from the information in the EU ARs but maintain their own regulatory responsibilities for decision-making.

Currently the pilot involves EU authorities as well as Health Canada, Swissmedic, the Taiwan Food and Drug Administration (TFDA) and the Therapeutic Goods Administration (TGA) of Australia. Other members of the IGDRP may decide to take part at a later stage.

In January 2015, the information-sharing pilot was extended to include applications for generics submitted through the Centralised Procedure, allowing EMA to share its ARs relating to these submissions with the collaborating non-EU regulatory agencies in real time.

The EU is leading this initiative with the aim of strengthening the scientific assessment, increasing consistency in the assessment of generics and saving global assessment resources.

WHO collaborative registration pilot for stringently authorized products, including through the EU’s Article 58 Procedure

The World Health Organization (WHO) collaborative registration pilot for medicines approved by a stringent regulatory authority (SRA) was initiated in 2015 as an extension of a WHO procedure that facilitates and accelerates the national registration of products already assessed and prequalified by WHO. The pilot aims at facilitating the registration of SRA-approved essential medicines in countries where regulatory

---

2 https://www.igdrp.com/
Regulatory collaboration

resources may be limited. Here as well, the receiving competent authorities retain their regulatory responsibilities and make their own decisions.\(^4\)

Since November 2014 EMA has participated in the development and implementation of the pilot. In this context, EMA ARs are shared with regulators in African countries by companies holding EU marketing authorizations who wish to market their products in these countries. EMA confirms, upon request from the company, that it has no objections to the sharing of its ARs and, in accordance with WHO procedures, confirms that the Quality Information Summary provided by the company complies with the information in the dossier assessed by EMA. EMA can provide the receiving authority with further information or clarification on any aspect of the assessment and promotes dialogue between the receiving authority and the relevant EMA assessors as required.

At the time of writing, EMA participation has involved three Centrally Authorized Products and one assessed under Article 58 (see below), for the treatment of HIV, malaria or tuberculosis.

Article 58 of Regulation (EC) No. 726/2004 (4) allows EMA’s Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the WHO, on medicinal products for human use that are intended exclusively for markets outside the EU. This includes vaccines used in the WHO Expanded Programme on Immunization, medicines used to treat public health priority diseases, and medicines for WHO target diseases such as HIV/AIDS, malaria or tuberculosis. Under Article 58 the CHMP carries out a scientific assessment according to the same standards as it would for Centrally Authorised Products authorized for marketing in Europe, taking into account possible different conditions of use. Experts and observers from WHO or from WHO Member States (appointed by WHO) are part of the assessment process. The CHMP, after consultation with WHO, adopts a scientific opinion, following the process in place for the Centralised Procedure.\(^5\)

An Article 58 Procedure followed by collaborative registration provides a useful approach to speeding up patient access to essential medicines, including new or improved therapies for unmet medical needs, without compromising on the quality of assessment.

Other uses of EU assessment reports by non-EU regulators

Non-EU regulators often request applicants to provide EU ARs in contexts other than the information-sharing initiatives described above. The use of EU ARs in the receiving country may be included in the legislation, guidelines or procedures of these countries. Some examples are given below.

**Switzerland**

The Swiss legislation (5) foresees that for a medicinal product which has already been granted an authorization in a country with a comparable control system for medicinal products, the assessment by the reference authority will be taken into account by Swissmedic during the authorization procedure, provided that the applicant explicitly requests Swissmedic to do so. The goal is to make medicinal products already authorized in

\(^4\) More information is available at http://apps.who.int/prequal/ under “Collaborative Registration”.

foreign countries available to patients in Switzerland as rapidly as possible while ensuring a targeted, risk-assessed use of Swissmedic’s resources.

Use of an existing EU AR in this way has decreased the review time by up to about 20%. In 2015, about 15% of medicinal products with known active substances authorized in Switzerland were authorized taking into account ARs produced by EMA or an EU Reference Member State. In addition, there are products for which the approval decision is not based solely on shared EU reports. Applicants are encouraged to always submit any such ARs as they are considered a valuable source of information.

**Canada**

In Canada, a draft guideline was published in 2012 (6) which details how information submitted by applicants on reviews carried out by foreign authorities can be used by Health Canada during the assessment of applications. The guideline recognizes that the Canadian law does not prevent Health Canada from using, where appropriate, foreign reviews to perform part of the evaluation or to inform Health Canada’s decision-making. Health Canada however cannot grant (or refuse to grant) marketing authorization based solely on the existence of a foreign review and its corresponding regulatory decision.

Different levels of reliance on foreign reviews are detailed in the guideline, allowing for the possibility that a critical assessment of the foreign review is used as a basis for the Canadian regulatory decision on the entire data package or on one or more of its components.

**Singapore**

Legislation in Singapore (7) allows for leveraging of foreign reports to grant marketing authorizations. The reference agencies accepted by the Singapore Health Sciences Authority (HSA) are EMA, U.S. FDA, Health Canada, TGA and MHRA (for national products or Decentralised and Mutual Recognition products where MHRA is the Reference Member State). For applications that have obtained prior approval from these reference agencies, HSA has a system that enables leveraging of assessments performed by these agencies, called the Verification Route (VR). To be eligible for the VR, one of the criteria is that the product is authorized for marketing in any two of the HSA’s reference agencies.

The VR takes 60 days (excluding clock-stops) as opposed to the 270 days necessary for products not previously authorized by any other authority (Full Route) or to the 180 days for products authorized by at least one drug regulatory authority (Abridged Route). 5% of the products authorized in Singapore in 2015 have been authorized via the VR using EMA assessment reports.7

**Mexico**

In 2012, EMA was approached by the Mexican medicines regulator COFEPRIS to facilitate an assessment of legal equivalence between the Mexican and EU pharmaceutical legislation. After dialogue with EMA lawyers, the result was a unilateral agreement (“acuerdo”) (8) through which Mexico uses the work carried out at EMA during assessment of Centrally Authorised Products to expedite approval of new medicines in Mexico. Similar arrangements are in place between Mexico and some other

---

6 Personal communication received from Swissmedic

7 Personal communication received from HSA
countries, including the United States, Canada, Australia and Switzerland.

Modalities for exchange of information with non-EU regulators

Sharing of assessment reports (ARs)

EMA ARs (for both the Centralised and the Article 58 procedures) and ARs from other agencies in the EU network are shared with non-EU regulators directly or through the marketing authorization holder.

Although EU ARs include commercially confidential information, they can be exchanged by EMA and the other agencies in the EU network with other regulators when there is a Confidentiality Arrangement in place between the EU and the receiving authority. Through these arrangements the parties agree not to disclose confidential information.

In the absence of such an agreement, unredacted EU ARs can still be exchanged directly with non-EU regulators, provided that the marketing authorization holder for the products consents to the exchange. EMA is encouraging such direct exchanges as far as possible, and a template to be used by companies to consent to exchange of ARs has been made public on the EMA website. EU ARs can also be provided by EU authorities without consent from the marketing authorization holder, but in these cases confidential information is redacted.

When marketing authorization holders are requested by a non-EU authority to share EU ARs for their products, they may ask the relevant EU agency to confirm in writing that it has no objection to the sharing. Unless there are serious reasons to object, the EU agency indicates to the company concerned that it does not object. A standard wording for responding to such requests has been developed and published on the EMA website.

Public ARs

Notwithstanding the measures identified above the EU assessment process is exceptionally transparent, and the possibility of taking advantage of what is made public on the websites of EMA and the other agencies in the EU network should not be underestimated. The EMA website, for example, is continuously updated with information on the quality, safety and efficacy of Centrally Authorised Products. For every medicine, including those with a positive opinion under Article 58, a European Public Assessment Report (EPAR) is published, which gives a wealth of information on the product, its use and its assessment. EMA also publishes information on medicines which receive a negative opinion from the CHMP.

Similar public ARs are published by other agencies in the European network. Public ARs for products assessed through the Mutual Recognition Procedure are published in the MR Product Index on the Heads of Medicines Agencies website.

---

8 Confidentiality Arrangements are in place between the EU and the following organizations: US Food and Drug Administration (FDA); Health Canada (HC); Japan Ministry of Health, Labour and Welfare (MHLW) and Pharmaceutical and Medical Devices Agency (PMDA); Swissmedic; Australia Therapeutic Goods Administration (TGA); World Health Organization (WHO)

9 Available in the EMA questions and answers on pre-submission guidance, Question No. 68 at: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000157.jsp

10 More information on EPARs is available at: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125

11 Available at: www.hma.eu/mrirproductindex.html
Additional approaches
Exchange or publication of ARs are not the only ways in which cooperation on medicine assessment among regulators can be achieved or information on assessment can be exchanged. Other possibilities are being explored, such as allowing regulators from other jurisdictions to listen to, or participate in, relevant product-specific meetings and discussions. The possibility of post-authorization webinars, where the scientific rationale for the decisions taken by an agency is explained and discussed with other regulators, may also be considered.

Remaining barriers
There are still barriers to overcome in furthering the exchange of assessment and inspection information among regulators worldwide. Such barriers can be legal (e.g. lack of legal framework, confidentiality issues), technical (e.g. lack of secure IT platforms for information-sharing), and non-technical (e.g. political issues, lack of trust). However, none of them should be big enough to prevent cooperation and sharing of information among regulators, given the benefits it can bring to patients worldwide.

EMA and the other agencies in the EU network are committed to finding ways to overcome such barriers wherever they exist. For example, in the absence of a globally accepted secure IT platform, they share unredacted ARs through the EU secure email system, Eudralink, which is encrypted and password-protected. Multilateral cooperation forums such as WHO groups and committees, the International Conference of Drugs Regulatory Authorities (ICDRA), the International Coalition of Medicines Regulatory Agencies (ICMRA), the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and the International Generic Drug Regulators Programme (IGDRP) among others provide excellent platforms for working together to overcome remaining difficulties.

Conclusion
The challenges faced by regulators in an increasingly complex regulatory environment are shared and recognized by the EU agencies network, and the need for cooperation is emphasized in the recently published EU network strategy (1). EMA and the other agencies in the EU network are willing to provide support and to cooperate with other international regulators as much as possible, while at the same time benefiting from the work done by other authorities as far as possible.

As demonstrated by examples from other regions of the world, the EU authorities are not alone in favouring and promoting sharing of ARs and other regulatory documents (e.g. inspection reports). However, such cooperation is currently mainly carried out at regional level. It makes little sense that the work carried out by regulators in one part of the world is not shared with regulators in other regions. The cooperation and sharing need to be more global in order to be more effective.

It has become increasingly clear that forms of cooperation requiring a strong legal framework often require a very long time to be achieved. An alternative approach is that of reliance, in which regulatory authorities make use of shared information but retain their decision-making responsibilities. Reliance can be unilateral, bilateral or multilateral, can be achieved in a short timeframe, does not require a heavy legal framework, and can
be the prelude to more formalized forms of cooperation such as mutual recognition agreements.

To promote reliance and work-sharing in line with the EU network strategy to 2020, EMA and the other agencies in the EU network will continue to share unredacted EU assessment and inspection reports with other regulators worldwide as much as possible, and will actively develop new and better ways to facilitate cooperation and exchange of information to realize the greatest possible benefits for patients.

References
1 EMA. EU Medicines Agencies Network Strategy to 2020. Working together to improve health. London: European Medicines Agency; 17 December 2015. Available at:
2 AMRH. 2nd Task Team meeting to facilitate the establishment of African Medicines Agency (AMA) successful. AMRH Newsletter January–June 2016; pp. 5-6.
5 Swiss Confederation. Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA) of 15 December 2000. Article 13, Medicinal products authorised in foreign countries, and Ordinance of 17 October 2001 concerning Medicinal Products (Medicinal Products Ordinance), Articles 5a - 5d.
7 Health Sciences Authority (HSA). Guidance on medicinal product registration in Singapore. Effective 1 April 2011.
Medicines regulation

Comparison of medicines legislation in the East African Community

Efficient and aligned regulatory systems are crucial in ensuring access to medical products of assured quality. However, marketing authorizations of needed products are often delayed as researchers and manufacturers must navigate multiple regulatory requirements to register their products across countries.

In the East African Community (EAC), efforts are under way for harmonization of technical requirements for medicines regulation. This article presents a comparison of legal and regulatory frameworks for the regulation of medicines in EAC partner states. The findings show some commonalities but also differences and gaps, underlining the need for convergence towards a common medicines regulatory framework in line with international standards.

Background

East African Community

The East African Community (EAC) was established in 1999 among the Republics of Kenya, Uganda, Rwanda, Burundi and the United Republic of Tanzania. With a population of 161.3 million people in 2015 it is home to approximately 14% of the population of the African continent. Life expectancies are below the global average, and all EAC partner states except Kenya are low-income countries according to the World Bank classification (Table 1).

Table 1: Demographic characteristics of EAC partner states

<table>
<thead>
<tr>
<th>Partner state</th>
<th>Land size, km²</th>
<th>Population, million</th>
<th>Gross domestic product (GDP), million US$</th>
<th>Gross national income (GNI) per capita*, US$</th>
<th>Life expectancy at birth**, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya</td>
<td>569 140</td>
<td>46.1</td>
<td>63 398</td>
<td>1 340</td>
<td>63.4</td>
</tr>
<tr>
<td>Tanzania</td>
<td>855 800</td>
<td>53.5</td>
<td>44 895</td>
<td>910</td>
<td>61.8</td>
</tr>
<tr>
<td>Rwanda</td>
<td>24 670</td>
<td>11.6</td>
<td>8 096</td>
<td>700</td>
<td>66.1</td>
</tr>
<tr>
<td>Uganda</td>
<td>200 520</td>
<td>39.0</td>
<td>26 369</td>
<td>670</td>
<td>62.3</td>
</tr>
<tr>
<td>Burundi</td>
<td>25 680</td>
<td>11.2</td>
<td>3 085</td>
<td>260</td>
<td>59.6</td>
</tr>
</tbody>
</table>

* The World Bank defines low-income economies as those with a GNI per capita of up to US$ 1 025. Lower middle-income economies are those with a GNI per capita of US$ 1 026-4 035.

** Global average 2015: 71.4 years.

This article was authored by Mr. Hiiti B Sillo, Tanzania Food and Drugs Authority (TFDA), with input from Mr Sunday Kisoma, TFDA, and Mrs Monika Zweygarth. We thank Professor Eliangiringa Kaale and Professor Veronica Mugoyela from Muhimbili University of Health and Allied Sciences, Tanzania, and Dr Lembit Rägo from the Council for International Organizations of Medical Sciences (CIOMS), Switzerland, for helpful comments on the manuscript.
Medicines regulatory harmonization

Harmonization initiatives for regulation of medicines started in 1990 when the medicines regulators and the research-based industry of Europe, Japan and United States of America established the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, now known as the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). The objectives of ICH are to improve the efficiency of drug development and registration processes. To date, ICH has published guidelines in all areas of medicines regulation including 12 quality guidelines, 11 safety guidelines, 18 efficacy guidelines and 8 multidisciplinary guidelines (1).

One example of a functioning and successful regional harmonization initiative is that implemented by the European Union (EU), which offers several registration pathways (2). Under the EU centralized procedure, pharmaceutical companies submit a single marketing authorization application to the EMA. The relevant Committee carries out a scientific assessment of the application and gives a recommendation on whether or not to grant a marketing authorization. Once granted by the European Commission, the centralized marketing authorization is valid in all EU member states. Under the decentralized procedure, applications are submitted and subsequently approved simultaneously in several member states, one of which is designated as the “reference member state”. Under the mutual recognition procedure, which is applicable to the majority of conventional medicinal products, already existing national marketing authorizations are recognized by one or more EU member states. National authorizations are still available for medicinal products to be marketed in one EU member state only.

Other regional harmonization initiatives are under way in the Association of the Southeast Asian Nations (ASEAN), the Gulf Cooperation Council (GCC), the Pan American Network for Drug Regulatory Harmonization (PANDRH) and the Southern African Development Community (SADC).

EAC medicines regulation harmonization

Chapter 21, Article 118 of the EAC Treaty (3) provides for co-operation on health and specifically asks partner states to harmonize drug registration procedures so as to achieve good control of pharmaceutical standards without impeding or obstructing the movement of pharmaceutical products, and hence facilitate access to pharmaceutical products within the Community. This is expected to increase access to medicinal products needed to treat health conditions that are prevalent in the region.

The beginnings of harmonization of medicines regulation in the EAC region go back to 2001, when the technical requirements for registration of veterinary drugs were approved by the EAC national medicines regulatory authorities (NMRAs) as exemplified by the Tanzanian guidelines. This was followed by a situation analysis of partner states (4), which highlighted some differences in regulatory capacity and scope of activities as well a lack of institutional mechanisms to share information for example on drug registration or product recalls.

The EAC Medicines Regulation Harmonization (MRH) Programme was launched in March 2012. It was the first programme to receive funding under the African Medicines Regulatory
Harmonization (AMRH) initiative through a trust fund established by an agreement between the Bill & Melinda Gates Foundation and the World Bank. The ultimate goal of the EAC MRH programme is to establish a harmonized regulatory system in the region that enables approval of medicines through various regulatory pathways, similar to the regulation model implemented by the EU Member States.

**EAC medicines regulatory systems**

**Medicines laws**

An overview of the medicines regulatory framework in EAC partner states is shown in Table 2. Some specific aspects are compared below.

**Scope of regulation**

The national medicines regulatory authority (NMRA) of Uganda regulates medicines only, and this includes oversight

### Table 2: Legal framework for medicines regulation in EAC partner states

<table>
<thead>
<tr>
<th>Partner state</th>
<th>Medicines law</th>
<th>Year of Enactment</th>
<th>Amendments</th>
<th>Regulatory authority</th>
<th>Organizational set-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burundi*</td>
<td>Décret n° 100/150 du 30 septembre 1980 portant Organisation de l'exercice de la Pharmacie au Burundi</td>
<td>1980</td>
<td>None</td>
<td>Department of Pharmacy, Medicines and Laboratory (DPML)</td>
<td>Department under the Ministry of Public Health and the Fight against HIV and AIDS, Head: Director</td>
</tr>
<tr>
<td>Kenya</td>
<td>The Pharmacy and Poisons Act, Chapter 244</td>
<td>1957</td>
<td>2009</td>
<td>Pharmacy and Poisons Board (PPB) <a href="http://www.pharmacyboardkenya.org">www.pharmacyboardkenya.org</a></td>
<td>Statutory body under the Department of Ministry of Health; Head: Registrar and Chief Pharmacist</td>
</tr>
<tr>
<td>Rwanda</td>
<td>Law No. 47/2012 of 14/01/2013 relating to the Regulation and Inspection of Food and Pharmaceutical Products</td>
<td>2013</td>
<td>None</td>
<td>Pharmaceutical Services (Pharmacy Taskforce)</td>
<td>Unit of the Department of Clinical Services in the Ministry of Health; Head: Head of Pharmaceutical Services</td>
</tr>
<tr>
<td>Tanzania (Mainland)</td>
<td>Tanzania Food, Drugs and Cosmetics Act, Cap 219</td>
<td>2003</td>
<td>2004, 2014</td>
<td>Tanzania Food and Drugs Authority (TFDA) <a href="http://www.tfda.or.tz">www.tfda.or.tz</a></td>
<td>Government Executive Agency, Head: Director-General</td>
</tr>
<tr>
<td>Tanzania (Zanzibar)</td>
<td>The Zanzibar Food, Drugs and Cosmetics Act</td>
<td>2006</td>
<td>None</td>
<td>Zanzibar Food and Drugs Board (ZFDB) <a href="http://www.zfdb.go.tz">www.zfdb.go.tz</a></td>
<td>Statutory Board under the Ministry of Health; Head: Registrar</td>
</tr>
<tr>
<td>Uganda</td>
<td>The National Drug Policy and Authority Act</td>
<td>1993</td>
<td>None</td>
<td>National Drug Authority (NDA) <a href="http://www.nda.or.ug">www.nda.or.ug</a></td>
<td>Semi-autonomous organization under the Ministry of Health; Head: Executive Director/Registrar</td>
</tr>
</tbody>
</table>

* In Burundi a law relating to regulation of medicines was at the draft stage at the time of writing. This text was obtained from the national medicines regulatory officer and was reviewed for this comparison. No major changes were anticipated until its entry into force. In addition, provisions for medicines registration were published in 2013 in a ministerial order (see Footnote 3 on Page 570 for details).
of the national drug policy and essential medicines list. In Kenya the NMRA also regulates poisons. The NMRA of Tanzania (Mainland and Zanzibar) regulate food, medical devices, cosmetics and herbal drugs in addition to pharmaceuticals. The law of Rwanda relates to the regulation and inspection of food and pharmaceutical products; however no food regulation is actually carried out. The draft law of Burundi mandates the NMRA to regulate drugs and other products whose consumption can harm health.

**Regulation of the pharmacy profession**

Regulation of pharmacy professionals – pharmacists, pharmaceutical technicians and pharmacy assistants – is included in the medicines laws of Kenya and Tanzania (Zanzibar). The laws of Uganda, Rwanda, and Tanzania (Mainland) and the draft medicines law of Burundi focus on regulation of medicinal products, while the pharmacy profession is governed by separate laws¹ and is regulated by the professional associations or councils.

**Licensing of activities and premises**

The laws of Kenya, Uganda, Rwanda and Tanzania (Zanzibar) contain provisions for licensing of retail and wholesale outlets as well as manufacturers of pharmaceuticals. The law of Tanzania (Mainland) covers licensing of manufacturing facilities and wholesale premises engaged in importation and exportation, whereas the regulation of wholesalers and retail outlets is governed by the Pharmacy Act, 2011² with the controls being implemented by the Pharmacy Council. The draft medicines law of Burundi does not include provisions for licensing of activities.

**Provisions for registration of medicines**

Five of the six medicines laws reviewed include detailed provisions for registration of medicinal products before they are placed on the market. The draft law of Burundi mentions the registration function as part of the Department’s mandate, while details were published in 2013 in a ministerial order³.

Provisions for importation of unlicensed medicines in special circumstances are found in the laws of Tanzania (both Mainland and Zanzibar), Kenya and Rwanda and in the 2013 ministerial order of Burundi. The law of Uganda is silent on this issue.

**Compliance with good manufacturing practice (GMP)**

Kenya, Tanzania (Mainland and Zanzibar) and Uganda have national guidelines on GMP based at a minimum on WHO GMP standards, and compliance with these guidelines is required for medicines registration in these countries. In Uganda, compliance with GMP guidelines is required for licensing of premises under the regulations on Certificate of Suitability of Premises, 2014⁴ of the National Drug

---


³ Rwanda: Law No 45/2012 of 14/01/2013 relating to the organization, functioning and competence of the National Pharmacy Council.

⁴ Burundi: Decrét no 100/150 du 30 septembre 1980, see also Table 1.

---

² see Footnote 1


⁴ Available at: http://www.nda.or.ug/files/downloads/Drug%20Certificate%20of%20
Act. The guidelines are detailed and in line with WHO’s current GMP standards, and the NMRA of Uganda is the lead agency on inspections of manufacturing facilities within the framework of EAC-MRH, which signifies the country’s level of strength in this area. The law of Rwanda requires that “pharmaceutical products ... are manufactured in compliance with relevant principles relating to their manufacture” and prohibits manufacture of pharmaceutical products without a license granted under the law; GMP compliance is mentioned in a comprehensive guideline on registration of medicines compiled by the Technical Working Group on Medicines Evaluation and Registration of the EAC MRH Programme, which was approved by the Minister and published on the website of the Ministry of Health of Rwanda in 2014. In Burundi, GMP certificates and GMP inspection are mentioned in the registration application forms, but not in the draft medicines law itself or in the 2013 ministerial order.

Quality control laboratories
In Tanzania (Mainland and Zanzibar) the laboratory is part of the NMRA with appropriate legal provisions. In Kenya there is a legal basis for the quality control laboratory, which is however set up as an independent body corporate with its own organizational structure and management, where the head of the laboratory does not report directly to the head of the NMRA. In Uganda the legal provisions are not explicit but implied and the laboratory is a core department of the NMRA. The quality control laboratories of Kenya, Uganda and Tanzania (Mainland) were the first in the EAC region, and all three are WHO-prequalified. Rwanda has a quality control laboratory under the Rwanda Standards Board under the Ministry of Trade, Industry and EAC Affairs. Burundi has a quality control laboratory under the National Institute of Public Health (INSP), but according to the national strategic plan for laboratory services 2015-2019 it does not currently serve as a national reference laboratory.

Pharmacovigilance
Although the laws of Kenya, Rwanda and Tanzania (Mainland and Zanzibar) mention the follow-up of medicines safety as one of the functions of the regulatory authority, they do not contain specific provisions for pharmacovigilance activities by the regulatory agencies. Nevertheless, in Kenya pharmacovigilance is being executed by the Pharmacy and Poisons Board of Kenya in line with specific guidelines found on the authority’s website, and in Uganda and Tanzania pharmacovigilance activities are also carried out by the respective NMRA. In Tanzania (Zanzibar) medicines safety is monitored by the Zanzibar Food and Drugs Board, while the TFDA is mandated to perform this function throughout the Mainland. The Pharmacy Task Force performs pharmacovigilance in Rwanda, although the medicines law of Rwanda is silent on this issue, as is the draft law of Burundi.

5 Available at: http://moh.gov.rw/fileadmin/templates/protocols/APPROVED_MOH_GUIDELINES_ON_SUBMISSION_OF_DOCUMENTATION_FOR_REGISTRATION_OF_HUMAN_PHARMACEUTICAL_PRODUCTS.pdf
7 Available at: http://pharmacyboardkenya.org/downloads/?file=national_pv_guidelines.pdf
Control of clinical trials
The laws of Tanzania (Mainland and Zanzibar) describe the approval process for clinical trials and include some provisions for informed consent, trial monitoring and reporting. Related regulations and guidelines are published on the TFDA’s website\(^8\). Similarly, the law of Kenya mentions the need to conduct clinical trials as a condition for registration of medicines to establish their safety, efficacy or bioequivalence as applicable, while a comprehensive guideline on clinical trials is available on the PPB’s website\(^9\). The law of Rwanda contains a general statement about the need for imported and domestically produced pharmaceutical products to undergo clinical trials to identify their effectiveness and potential adverse effects related to their use. However detailed provisions could not be found in the public domain either for Rwanda or for Burundi.

Provisions to make specific regulations
The laws of both Tanzania Mainland and Zanzibar enable the Minister of Health, on advice of the regulatory authorities, to make regulations pertaining to products and activities regulated under the respective medicines laws. The laws of Uganda (Section 61) and Kenya (Section 44) provide for making special regulations. The medicines laws of Rwanda and Burundi do not contain provisions to make regulations.

Sanctions
The medicines laws of Burundi and Rwanda do not contain specific provisions for sanctions to individuals or entities that contravene provisions made under the respective laws. The medicines laws of Kenya, Uganda, Tanzania (Mainland and Zanzibar) contain specific provisions for sanctions including monetary penalties, revocation of professional and/or product permits, confiscation of consignments and deportation and imprisonment. The maximum fines under the respective medicines laws are five million Tanzania Shillings (approx. 2 350 US$), 1 million Kenya Shillings (approx. 9 800 US$) and 1 million Uganda Shillings (approx. 300 US$), and the maximum terms of imprisonment are five years in Uganda, two years in Kenya and Tanzania (Mainland), and six months in Tanzania (Zanzibar).

Discussion
NMRAs are entrusted with ensuring the efficacy, safety and quality of medicines, and they are expected to carry out these tasks by applying the best available scientific knowledge and skills without bias. A recent achievement that can support regulatory strengthening and convergence in the region is the publication of the African Union Model Law on Medical Products Regulation (5), which covers the key principles of effective medicines regulation. The review of the medicines laws of EAC countries presented here has identified some differences and gaps that need to be addressed.

Organizational set-up
Good governance including accountability and transparency, sufficient competent human resources to carry out the required tasks, adequate financial resources and freedom from undue influence of politics and the interests of individuals, groups and the public are critical for
effective medicines regulation. Efficient, independent and unbiased decision-making therefore requires that a sound organizational structure is in place, giving the authority the power to acquire and use resources and to appoint and dismiss staff and determine the level of their remuneration. The AU Model Law recommends that authorities should be autonomous, although they should remain functionally and financially accountable to their Ministries. However, of the six regulatory bodies in EAC partner states only those of Tanzania (Mainland) and Uganda have autonomy in decision-making on staffing and finances. The other NMRAs are Boards or Departments that are dependent on resource allocation from the Ministry of Health, an arrangement that can affect the efficiency of regulatory activities.

Control of activities
Through licensing of activities, NMRAs are able to ensure that medicines are manufactured, stored, distributed and sold in premises complying with regulations and that they comply with the specifications of their marketing authorization until they reach the end users. The NMRAs of Kenya, Uganda and Tanzania (Zanzibar) are in charge of licensing the full range of activities and can institute appropriate measures to safeguard the quality of pharmaceuticals. In Tanzania (Mainland) the responsibilities are divided between the regulatory authority, which controls manufacturing and wholesale (importers’) premises, and the Pharmacy Council, which controls wholesalers and retail outlets. While this arrangement offers clustering of regulatory activities, it may result in loopholes and inefficiency in regulation, as the two parties have different objectives, standards, processes and reporting lines (6).

Pre-marketing control of products
Medicines registration is at the centre of the medicines regulatory functions. It involves the pre-marketing assessment of data submitted by applicants to establish the compliance of products with standards of quality, safety and efficacy. A clear presentation of the technical requirements for registration is important for effective enforcement, as it gives NMRAs the power to refuse registration or to remove products from registers. The laws of Kenya, Tanzania (Mainland and Zanzibar) and Uganda contain detailed provisions for registration of medicines with defined standards to be met in terms of quality, safety and efficacy. In Burundi and Rwanda the law contains a general clause, while detailed provisions were subsequently published in an Order of the Minister. These dispositions enable the EAC countries in principle to control the quality, safety and efficacy of the medicines placed on their markets.

To facilitate convergence of practices a detailed Medicines Evaluation and Registration Compendium was developed under the EAC-MRH programme (7). The compendium is based on the Modules of the ICH Common Technical Document (CTD) format and can be adapted for national use, as has been done in the guidelines published in 2014 in Rwanda. Currently, Tanzania through TFDA serves as a lead agency in Medicines Evaluation and Registration in the EAC, and so far work-sharing has been successfully demonstrated. Despite the effort made, technical capacity in assessment and registration especially of new chemical entities and biotechnology derived products still poses a challenge towards effective regulation.

Compliance with GMP was found to be a requirement for registration of
medicines in only three of the six laws reviewed. In the other countries provisions for GMP compliance were in the form of recommendations and guidance and may hence not be legally enforceable. This increases the risk that medicines are assessed and registered even though they are manufactured in facilities that do not comply with GMP. In such facilities there is a higher risk of mix-ups and cross-contamination of products, among other threats, with serious potential impact on the health of patients.

Post-market control of products
Quality control laboratories form an important component in effective regulation of medicines. Their role is to offer pre- and post-registration testing of product samples in order to confirm that a product conforms with its specifications at all times. Functional quality control laboratories are in place in Kenya, Tanzania, Uganda and Rwanda. While in Tanzania and Uganda both functions are under the same roof, in Kenya the laboratory is independent of the NMRA and in Rwanda it is under the Rwanda Standards Board. The latter arrangement facilitates independent analysis and reporting of analytical results without undue influence by findings from dossier assessment and inspections. However, it may affect the efficiency of communication and delay product registration, since pre-registration testing is a requirement for all pharmaceutical products in Kenya.

No quality control laboratory exists in Burundi. Regional collaboration could offer a solution, although cross-border shipment of samples under controlled conditions and communication of results may pose significant logistic and organizational challenges. The absence of quality control laboratories can therefore delay regulatory actions and impact the patients.

Pharmacovigilance is important to detect adverse events observed with medicines on the market. Although pharmacovigilance activities are being carried out in EAC countries, the absence of specific legal provisions in this area is likely to hinder the effective control of safety of registered medicines, as guidelines published by individual partner states may not be legally enforceable.

Control of clinical trials
Effective regulatory control of clinical trials is another important aspect of medicines regulation. For this purpose, laws must contain detailed provisions on how pharmaceutical companies should apply for permission to carry out clinical trials, and how NMRAs in collaboration with Ethics Committees should perform ethical and regulatory review, approve clinical trials, inspect clinical trial sites, and follow-up periodically on the conduct of the trials according to the approved protocols. The full range of the above-mentioned provisions was not found in all the medicines laws reviewed. However, an approval process for clinical trials exists in EAC countries, with detailed regulations and guidelines available in some of the partner states. Cooperation and capacity-building were stepped up when the need for clinical testing was urgent. During

10 Pre-registration testing can serve to verify that the manufacturer’s testing methods for the product give valid results at the national laboratory, but has otherwise been found to have little added benefit as it is rare to find product deficiencies in registration samples submitted by applicants. In recent years it has been recognized that the focus should be on targeted, risk-based testing as part of post-market surveillance to ensure that products circulating in countries comply with the specifications of their marketing authorization on an ongoing basis.
the Ebola crisis the African Vaccines Regulatory Forum (AVAREF) served as a common platform for regulators and ethics committee in reviewing and approving clinical trial applications (8).

**Enforcement of legal provisions**

Enforcement of medicines legislation depends to a large extent on the deterrent effect of sanctions. The fines and jail terms specified in the laws of EAC partner states are relatively low compared to the profits often realized by unlawful dealers of medicines, and are in no way commensurate to the risks that substandard and counterfeit medicines pose for the population. By contrast, in a small EU country with 1.4 million inhabitants, Estonia, dealers of medicines who contravene the provisions of the Medicines Act11 are liable to pay fines of up to 32 000 Euro (approximately US$ 35 700), and certain offenses are subject to prosecution and punishment under other laws, for example criminal law.

**Adaptation to change**

Provisions to make specific regulations enable governments to accommodate the need for new regulatory functions as they emerge. The AU Model Law on medical products regulation gives the supervisory authority (i.e. the Ministry in charge of health) the power to make regulations and guidelines necessary to pursue the objectives of the medicines law, in consultation with the regulatory authority. Clauses to this effect are included in the laws of Uganda, Kenya and Tanzania (Mainland and Zanzibar). The laws of Rwanda and Burundi are silent on this aspect, and this means that the agencies have to go through the often bureaucratic process of amendment of the main laws every time an update is necessary. The resulting loopholes may encourage acts of unlawful dealing in medicines, especially as the general statutory laws of EAC countries do not have adequate sanctions in place compared to the potential profit to be made by illegal activities.

**Limitations of this comparison**

The comparison presented in this article focused on the medicines laws of EAC partner states. It did not systematically take into account other laws or the full range of regulations that affect the control of medicines. Nevertheless, the findings identify the main gaps and opportunities for achieving effective regulation through harmonization and can thus be useful in improving the legal systems in EAC partner states as part of the ongoing EAC harmonization process.

The review focused on the main regulatory functions. In addition to providing for these, the AU Model Law includes some “Miscellaneous provisions” on management of conflicts of interest, the extent of liability of NMRAs for loss or damage arising from their decisions, and protection of and access to information. These aspects were not considered in this article, although they can have a direct impact on the control of medicines. For example, a review of WHO assessment reports of regulatory systems in African countries (9) found that in many cases medicines regulation is not sufficiently independent from the procurement function, and that there is limited public access to up-to-date registers of authorized products, licenced premises and professionals.

---

Conclusion
The medicines laws in EAC partner states cover most of the key regulatory functions, and NMRAs are in place. The laws are at different stages of implementation, with some partner states having significantly more regulatory capacity and experience than others. On the other hand, some of the older laws have not been recently reviewed or amended to keep up with the pace of pharmaceutical innovation and technology. Some NMRAs conduct key functions that are not provided for in their respective medicines laws.

Differences were found in the legal provisions for key regulatory functions as well as in regulatory practices of EAC partner states, potentially creating delays in bringing needed medicines to the populations and presenting legal loopholes that can easily be exploited. The sanctions stipulated in the laws are generally not severe enough, nor enforced to a sufficient extent, to deter unlawful dealing in medicines across the EAC region.

The differences and gaps need to be addressed in collaboration, since all EAC partner states are faced with similar health and economic challenges. Future challenges are likely to be experienced across the region as globalization and cross-border trade and travel increase. These developments call for convergence of regulatory practices in the region by streamlining the existing legal and regulatory frameworks towards a common medicines law in the region. The medicines regulatory harmonization programme in EAC partner states is a good start towards achieving this objective.

References
Safety news

Safety warnings

**DPP-4 inhibitors: Pemphigoid**

Japan – A warning about the risk of pemphigoid has been added to the approved product information in Japan for antidiabetics containing the dipeptidyl peptidase 4 (DPP-4) inhibitors alogliptin, linagliptin or teneligliptin. Health professionals are advised to refer patients with blisters, erosions or other signs or symptoms of this skin condition to a dermatologist, and to consider treatment discontinuation.

► PMDA Summary of investigation results and MHLW Revision of precautions, 22 November 2016.

**Polaprezinc: copper deficiency**

Japan – The PMDA has recommended that the risk of copper deficiency should be included in product information for polaprezinc, a medicine used to treat gastric ulcer.

Pancytopaenia and anaemia have been reported in Japan in poorly nourished patients treated with polaprezinc. These adverse effect may occur because the zinc contained in the medicine inhibits the absorption of copper. Health professionals should monitor their patients and take appropriate measures if any abnormalities are observed.

► PMDA Summary of investigation results, and MHLW Revisions of precautions, 22 November 2016.

**Brimonidine gel: worsening of rosacea symptoms**

United Kingdom – Prescribing advice for brimonidine gel (Mirvaso®) has been updated following an EU-wide review that found worsened rosacea symptoms in up to 16% of patients treated with brimonidine gel in clinical studies. In most cases, the erythema and flushing resolved after the treatment was stopped.

Treatment should be initiated with less than the maximum dose for at least one week, and the dose should be increased gradually based on tolerability and response to treatment. The maximum daily dose (1 g of gel in total weight, approximately 5 pea-sized amounts) should not be exceeded. Patients should be advised to stop treatment and consult a doctor if they notice increased redness or burning during treatment.


**Levonorgestrel emergency contraceptives: interactions with liver enzyme inducers**

United Kingdom – The MHRA has informed health professionals that women seeking emergency contraception who have used cytochrome P450 3A4 (CYP3A4) enzyme inducers (such as the antiretrovirals efavirenz and ritonavir, certain medicines for tuberculosis and epilepsy and herbal medicines containing St John’s wort) within the last four weeks should use a copper intrauterine device or, if this is not an option, double the dose of levonorgestrel from 1.5 mg...
to 3 mg. Ulipristal acetate emergency contraception is not recommended for use in these women. Advice should also be provided on highly effective ongoing contraception as described in national guidance.

This follows a review of the emergency contraceptive levonorgestrel (Levonelle® and associated names) by the EMA, which found that medicines or herbal remedies that induce CYP3A4 enzymes lower the blood levels of levonorgestrel, which may reduce its emergency contraceptive efficacy.

► MHRA Press release, 15 September 2016.
   EMA. Referrals. Levonelle 1500 microgram tablets and associated names.

Direct-acting antivirals: hepatitis B reactivation

United States of America — The FDA has warned health professionals that cases of hepatitis B virus reactivation have occurred in patients co-infected with hepatitis C virus while undergoing treatment with direct-acting antivirals (DAA). Some cases have resulted in fulminant hepatitis, hepatic failure and death.

A "Boxed Warning" is to be added to the product information of daclatasvir (Daklinza®), sofosbuvir and velpatasvir (Epclusa®), ledipasvir and sofosbuvir (Harvoni®), simeprevir (Olysio®), sofosbuvir (Sovaldi®), ombitasvir and paritaprevir and ritonavir (Technivie®), dasabuvir and ombitasvir and paritaprevir and ritonavir (Viekira Pak®, Viekira Pak XR®), and elbasvir and grazoprevir (Zepatier®), directing health care professionals to screen and monitor all patients receiving these medicines for hepatitis B virus. (1) The EMA, Health Canada and the TGA of Australia have performed their own reviews and have issued similar warnings (2, 3, 4). The EMA has confirmed its earlier recommendation to screen all patients for hepatitis B before starting treatment with DAAs, and has concluded that further studies are needed to assess the risk of liver cancer with these medicines.

► (1) FDA Drug safety communication, 4 October 2016.
   (2) EMA Press release, 16 December 2016.
   (3) Health Canada Advisory, 1 December 2016.
   (4) TGA Safety advisory, 19 December 2016.

HIV treatment-boosting agents and steroids: systemic adverse effects

United Kingdom — The MHRA has warned health professionals that the use of steroids metabolized by the cytochrome P450 3A (CYP3A) pathway in to patients treated with a HIV treatment-boosting agent may increase the risk of systemic corticosteroid-related adverse effects. Although these reactions are rarely reported, this interaction may occur even with steroid formulations administered by intranasal, inhaled, and intra-articular routes. Coadministration of these medicines is not recommended unless the potential benefit to the patient outweighs the risk. In such cases use of beclomethasone should be considered, particularly for long-term use, as it is less dependent on CYP3A metabolism. Patients should be monitored for systemic corticosteroid-related reactions.

► MHRA. Drug Safety Update vol 10 issue 5, December 2016: 1.
Nivolumab: immune thrombocytopenic purpura, myocarditis, rhabdomyolysis

Japan – The PMDA has recommended updates to the product information for the anti-cancer medicine nivolumab (Opdivo®) to warn about the risk of immune thrombocytopenic purpura, and about the risk of myocarditis and rhabdomyolysis, in addition to myasthenia gravis and myositis that are already mentioned as adverse effects. In the section on precautions, a statement has been added that patients should continue to be monitored after treatment discontinuation as serious adverse effects may still occur at that stage.

The revisions are based on reports of the above-mentioned events in people treated with nivolumab in Japan, and on reported cases of myocarditis and rhabdomyolysis in patients treated with nivolumab in other countries.

► PMDA Summary of investigation results and MHLW Revision of precautions, 18 October 2016.

Eculizumab: interaction with meningococcal vaccine

Canada – A Health Canada safety review has found that patients with complement-mediated diseases who were treated with eculizumab (Soliris®) had an increased risk of low haemoglobin, including anaemia or haemolysis, after vaccination with Serogroup B meningococcal vaccine (Bexsero®). The risk was highest in patients whose predicted systemic eculizumab concentrations were relatively low.

Health Canada has recommended that patients being treated with eculizumab should be vaccinated only after their disease has been controlled and within one week following eculizumab infusion, when the concentration of eculizumab in the blood is considered to be relatively high. Patients not yet treated with eculizumab should be vaccinated with a meningococcal vaccine (against serotypes A, C, Y, W135, and B) before or at the start of eculizumab treatment, unless the risks of delaying therapy outweigh the risks of developing a meningococcal infection. Patients who started eculizumab treatment less than two weeks after receiving a meningococcal vaccine should receive appropriate prophylactic antibiotics for two weeks after vaccination. The Canadian product information has been updated to include this new safety information.


Anaesthetics and sedatives in young children and pregnant women

United States of America – Based on a comprehensive analysis of published scientific studies, the FDA has issued a Drug Safety Communication to inform health care providers, parents and caregivers of children younger than three years, and pregnant women in their third trimester, that the repeated or lengthy (more than three hours) use of general anaesthetic and sedation medicines may adversely affect children’s developing brains. The FDA is requiring warnings to be added to the labels of these medicines. The Agency recognizes that in many cases these exposures may be medically necessary and that the potential harms must be carefully weighed against the risk of not performing a specific medical procedure.

► FDA Statement, 14 December 2016.

FDA Drug safety communication, 14 December 2016.
Known risks

**Pioglitazone: bladder cancer**
United States of America – The FDA has updated the labelling of products containing the type 2 diabetes medicine pioglitazone to describe the additional studies reviewed on the increased risk of bladder cancer in patients treated with pioglitazone. This follows warnings issued about this risk in 2010 and 2011.
► FDA Drug safety communication, 12 December 2016.

**Warfarin and miconazole: contraindicated**
Japan – The PMDA, in consultation with the MHLW, has approved an amendment to the product information for miconazole (gel and injection) and for warfarin, to include a contraindication for the two medicines to be used concomitantly due to the increased risk of bleeding.

Health professionals have been advised to prescribe other azole antifungal medicines. The product information for these alternative antifungals has also been updated to advise extreme caution and measures such as more frequent prothrombin time (PT) measurement and thrombotest, due to the increased PT-international normalized ratio (INR) in patients treated with warfarin and other azole antifungals.

These measures follow reports received in Japan of a substantial number of cases of serious bleeding during or after concomitant administration of the two drugs. The revision also took into account reports sent to the MHRA in the United Kingdom about possible interactions of warfarin and miconazole, including haemorrhagic events with fatal outcome. The MHRA is reviewing these data.

The approved product information for topical miconazole in the UK includes a warning that caution should be exercised in patients on oral anticoagulants such as warfarin, and anticoagulant effect should be monitored.
► PMDA Summary of investigation results, 18 October 2016.

**Statins: immune-mediated necrotizing myopathy**
Japan – The PMDA has recommended updates to the product information for statin-containing products on the market in Japan to warn about the risk of immune-mediated necrotizing myopathy.

In the EU, the approved product information for statins was updated in 2015 to include immune-mediated necrotizing myopathy as an adverse effect occurring with unknown frequency.
► PMDA Summary of investigation results, 18 October 2016.

EMA. PRAC recommendations on signals. Adopted at the PRAC meeting of 6-9 January 2015.

**Daptomycin: acute generalized exanthemous pustulosis**
Japan – The PMDA has recommended to update the product information for the antibacterial medicine daptomycin to warn about the risk of acute generalized exanthemous pustulosis (AGEP). This follows cases of AGEP reported both in Japan and elsewhere.

Approved product information in the EU includes a warning about AGEP, while the U.S. FDA-approved product information mentions that serious skin reactions, including Stevens-Johnson syndrome and
vesiculobullous rash, have been observed in the post-marketing phase.

► PMDA Summary of investigation results and MHLW Revision of precautions, 18 October 2016.

NSAIDs: increased risk of miscarriage

Australia – The TGA has completed a safety review on the known association between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the increased risk of miscarriage. The review focused on ensuring that consistent information on this risk was available for all products. The findings confirmed a potential increased risk of miscarriage with non-aspirin NSAIDs, particularly when the medicine is taken close to the time of conception. For aspirin the evidence was not sufficient to confirm an association with the risk of miscarriage.

The TGA is working with sponsors of non-aspirin NSAIDs to harmonize the warnings included in the product information in line with the conclusions of the review.

► TGA Safety advisory, 11 October 2016.

Paracetamol: updated labelling to address risk of liver injury

Canada – Health Canada has released an updated labelling standard for over-the-counter paracetamol (U.S. adopted name: acetaminophen), which provides clearer instructions and stronger warnings to help reduce the potential for liver damage. This follows a safety review completed in 2015, which found that more than half of the paracetamol-related cases of serious liver injury reported in Canada were associated with unintentional overdoses.

► Health Canada Information update, 15 September 2016.

Lurasidone and certain ARVs: contraindicated

United States of America – The FDA has announced that product information for several antiretrovirals (ARVs) has been updated to add lurasidone (Latuda®), an antipsychotic medicine, to the section on contraindications due to the potential for serious and life-threatening reactions. The ARVs concerned are: tipranavir, indinavir, saquinavir, ritonavir (also in combination with lopinavir), fosamprenavir (if co-administered with ritonavir), darunavir, atazanavir (if co-administered with ritonavir), nelfinavir, and fixed-dose combinations of elvitegravir, cobicistat, emtricitabine and tenofovir. Lurasidone is already included as a contraindicated medication in the product information of atazanavir/cobicistat and darunavir/cobicistat.

In the EU, approved product information for lurasidone includes a contraindication with strong CYP3A4 inhibitors, mentioning some of the above ARVs, and product information for the ARVs warns against co-administration of certain substances that are highly dependent on the CYP3A4 pathway for clearance.

► FDA HIV update bulletin, 19 September 2016.

Labelling changes

Metformin for patients with moderate kidney impairment

European Union – The EMA has completed a review of the antidiabetic metformin and has concluded that the
medicine can be given to patients with type 2 diabetes that have moderately reduced kidney function (glomerular filtration rate of 30–59 ml/min). Reduced doses should be considered for these patients according to the dosage recommendations to be provided in the updated product information. The contraindication for patients with severely reduced kidney function (glomerular filtration rate less than 30 ml/min) will remain.

Previously, metformin had not been recommended in patients with impaired kidney function because of the risk of lactic acidosis. The review found that the large patient population with moderately reduced kidney function can benefit from the use of metformin. Product information for metformin-containing medicines approved in the EU is being revised and harmonized to reflect current scientific evidence and recommendations.

► EMA Press release, 14 October 2016.

**Improved dosing instructions**

**Levetiracetam oral solution**

European Union – Cases of accidental overdoses with levetiracetam oral solution (Keppra®) have been reported in Europe, with the majority of cases occurring in children aged between 6 months and 11 years. Where the cause of the reported overdosing could be determined, it was either due to the use of an inappropriate syringe or the misunderstanding of the caregiver about how to measure the dose.

The EMA has recommended new measures to ensure the safe use of levetiracetam oral solution. Different colours will be used for the outer packaging and bottle labels of the different presentations. Prescribers should ensure that they prescribe the age-appropriate presentation of the medicine, indicating the dose in mg with a ml equivalence based on the correct age of the patient. Pharmacists should ensure that the appropriate presentation is dispensed. With every prescription, healthcare professionals should advise the patient and/or caregiver on how to measure the prescribed dose, reminding them to use only the syringe included in the package with each bottle and to discard the syringe once the bottle is empty.

► EMA Press release, 14 October 2016.
Unchanged recommendations

**Urine- and plasma-derived medicines: safe regarding Zika**

**European Union** – The EMA has confirmed that there is no increased risk of contamination with the Zika virus for patients who take plasma-derived medicines such as coagulation factors or immunoglobulins, or urine-derived medicines such as certain hormone-based treatments or urokinase products.

A review of information showed that the manufacturing processes used for plasma-derived products, such as the solvent/detergent method to inactivate viruses, liquid heat inactivation and virus filtration, inactivate or remove the Zika virus from the finished product. Likewise, manufacturing processes for urine-derived products contain complementary steps with inactivation/removal capacity for enveloped viruses, which are considered sufficient to ensure the Zika virus safety of these products. The EMA concluded that no additional safety measures such as screening, testing, deferral or exclusion of certain donors are necessary.


**EMA/CHMP Biological Working Party (BWP). Report on viral safety of plasma- and urine-derived medicinal products with respect to Zika virus. 15 September 2016.**

Non-compliance with good practices

**Pharmaceuticals International Inc., U.S.: import stop to EU**

**European Union** – The EMA has recommended that medicines manufactured by Pharmaceuticals International Inc., United States, should no longer be supplied in the EU. The only exception is sodium phenylbutyrate (Ammonaps®), a medicine used to treat urea cycle disorders which is considered to be critical for public health. In countries where alternatives are available Ammonaps® will be recalled. Certain other medicines supplied by Pharmaceuticals International Inc. are available from alternative registered manufacturing sites and will remain available in the EU.

These precautionary measures follow a review that was triggered by inspection findings of continued non-compliance with good manufacturing practice.

► EMA Press release, 16 September 2016.

Safety reviews started

<table>
<thead>
<tr>
<th>Under review</th>
<th>Concerns</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medicine:</strong> Certain injectable methylprednisolone products used to treat severe, rapidly developing (acute) allergic reactions</td>
<td>Traces of cows’ milk proteins could affect treatment of acute reactions in the small number of highly sensitive patients allergic to lactose. The reaction to the medicine may be mistaken for a worsening of the original condition, leading to additional doses of the medicine being given.</td>
<td>► EMA. Article 31 Referral started. EMEA/H/A-31/1449. 1 December 2016.</td>
</tr>
<tr>
<td><strong>Contract research organization:</strong> Micro Therapeutic Research Labs, India</td>
<td>Inspection findings of non-compliance with good clinical practice at the study sites in Chennai and Coimbatore, India</td>
<td>► EMA. Article 31 Referral started. 16 December 2016.</td>
</tr>
</tbody>
</table>
Regulatory news

Pre-market assessment

**EMA publishes clinical reports**

European Union – The EMA has started to give open access to clinical reports for new medicines for human use authorized in the EU on a new website, following the adoption of a new policy after extensive consultation with stakeholders. The website will include the clinical reports contained in applications for marketing authorization submitted to the Agency on or after 1 January 2015, and in applications for extension or modification of an indication, or for line extension, submitted on or after 1 July 2015. The data is intended to increase transparency, facilitate independent re-analysis and support efficient medicine development.

Data for two medicines were published initially, comprising over 100 clinical reports. EMA expects to offer access to approximately 4500 clinical reports per year. (1)

Data for two additional medicines followed one month later. (2)

Health Action International (HAI) has welcomed the move and has emphasized its strong support for the principle that clinical trial data must be made publicly available to all. (3)

► (1) EMA Press release, 20 October 2016.
(2) EMA Press release, 24 November 2016.

(3) HAI. Clinical Trial Data Transparency on Trial – EMA Under Pressure From Pharma Lawsuit. 1 December 2016.

Post-market surveillance

**Social media campaign on reporting of medicines side effects**

United Kingdom, European Union – On 7–11 November 2016 the MHRA held a social media campaign to promote reporting of suspected side effects as part of an EU-wide awareness week. Twenty-two EU Member States took part in the combined cross-European social media campaign organized under the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action project, which aims to raise awareness of national reporting systems for suspected side effects in medicines.


**EU project to strengthen market surveillance for medical devices**

Bratislava, Slovakia – At the 39th meeting of the EU Competent Authorities for Medical Devices (CAMD) held in Bratislava in October 2016, the MHRA launched the Joint Action on Market Surveillance of Medical Devices. Post-marketing surveillance is a crucial part of health product regulation to make sure that medical devices are acceptably safe and perform as intended. The project aims to improve the coordination of surveillance activities by EU member states and to ensure adequate communications and cooperation.

EU–U.S. collaboration on medicines for rare diseases

European Union, United States of America – The EMA and the FDA have set up a new working group to share experiences and best regulatory practices in the development of medicines for rare diseases. Global collaboration in this area is particularly important to ensure that the few studies that can be conducted in the small patient populations can benefit all patients. The agencies will exchange information on topics such as the design of clinical trials and the use of statistical analysis methods, the selection and validation of trial endpoints, preclinical evidence to support development programmes, the design of post-marketing studies, and risk management strategies for long-term safety issues.

The existing EMA/FDA “Cluster on orphan medicinal products” will continue to focus on orphan designation and exclusivity.

► EMA News, 26 September 2016.

Mapping of global medicines regulatory initiatives

European Union – The EMA has published a comprehensive overview of global initiatives on medicine regulation. The mapping was carried out by EMA on behalf of the International Coalition of Medicines Regulatory Authorities (ICMRA). The aim of the mapping exercise was to raise awareness of ongoing activities, provide a basis for strategic coordination and identify possible gaps.

The report was presented at the 11th Summit of Heads of Medicines Regulatory Agencies and the annual ICMRA meeting held in Interlaken, Switzerland, on 11-13 October 2016. It includes wide-ranging activities such as the harmonization work of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and identifies areas of particular strategic interest for ICMRA including generic medicines, good manufacturing practice inspections, exchange of confidential information, supply-chain integrity, crisis management, pharmacovigilance and information technology systems.


EMA. Connecting the dots. Towards global knowledge of the international medicine regulatory landscape: mapping of international initiatives. 2016.
MHRA and Swissmedic sign agreement

Interlaken, Switzerland – The MHRA and Swissmedic have signed a Memorandum of Understanding (MoU). The agreement was signed on the sidelines of the 11th Summit of the Heads of Medicines Regulatory Agencies in Interlaken, Switzerland. It focuses on implementing a shared approach to complex challenges and on promoting each other’s regulatory frameworks, requirements and processes, as a basis for information-sharing.

Swissmedic Announcement, 11 October 2016.

Use of medicines

Report on sales of veterinary antibiotics in Europe

European Union – The Sixth report on the sales of veterinary antibiotics in Europe highlights a slight downward trend, suggesting that actions taken by EU member states to fight antimicrobial resistance are making a difference.

A total of 28 countries reported data to the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) for the year 2014. While a considerable increase was noted in one European country due to an improvement in data collection systems, an overall decrease of 12% was found in 24 of the 25 countries that provided data for this four-year period. Other countries also changed their reporting systems or identified under-reporting, meaning that the findings should be interpreted with caution.

► EMA News, 14 October 2016.
EMAsales of veterinary antimicrobial agents in 29 European countries in 2014. Sixth ESVAC report.

Indian FDC ban reversed

India – The Delhi High Court has stayed a government ban on 344 fixed-dose combination (FDC) medicines after more than six months of hearing more than 300 petitions filed by pharmaceutical companies. (1)

The ban, which affected analgesic and antibiotic combinations among others, had been announced in March 2016 in the interest of public health. (2)


Under discussion

European Union – The European Medicines Agency (EMA) has published a revised guideline on first-in-human clinical trials. The revision was based on a concept paper released for comment earlier in 2016 and took into account the lessons learnt from the tragic incident which occurred during a clinical trial in Rennes, France, in January 2016. The revised guideline is open for public consultation until 28 February 2017.


European Union – The European Commission (EC) is seeking views and feedback from stakeholders, to support the Commission in drafting its second report on the Paediatric Regulation after ten years of implementation. The consultation is open until 20 February 2017.

Approved

**Obeticholic acid for rare, chronic liver disease**
- **Product name**: Ocaliva®
- **Dosage form**: Tablets
- **Class**: Bile acid preparation; 
  *ATC code*: A05AA04
- **Approval**: EMA (orphan product; conditional approval)
- **Use**: In combination with ursodeoxycholic acid (UDCA), treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in patients who cannot successfully be treated with UDCA alone.
- **Benefits**: Ability to delay development of liver fibrosis, cirrhosis liver transplant and death through reduction of alkaline phosphatase and bilirubin levels in adults with primary biliary cholangitis. The efficacy remains to be formally demonstrated by means of post-authorization follow-up.
- **Note**: In the past, the only option for these patients has been a liver transplant.

**Insulin aspart for diabetes mellitus**
- **Product name**: Fiasp®
- **Dosage form**: Solution for injection
- **Class**: Fast-acting insulin analogue; 
  *ATC code*: A10AB05
- **Approval**: EMA
- **Use**: Treatment of diabetes mellitus in adults
- **Benefits**: Ability to control blood glucose.
- **Note**: Fiasp® is an ultra-rapid-acting formulation of insulin aspart.
  - EMA CHMP Summary of opinion, 10 November 2016.

**Insulin glargine/lixisenatide for diabetes mellitus**
- **Product name**: Suliqua®
- **Dosage form**: Solution for injection
- **Class**: Fixed-ratio combination of insulin glargine, a basal insulin analogue, and lixisenatide, a glucagon-like peptide 1 (GLP-1) receptor agonist
- **Approval**: EMA
- **Use**: In combination with metformin, treatment of diabetes mellitus in adults when glycaemic control has not been provided by other treatments.
- **Benefits**: Clinically relevant effect on glycaemic control in patients with type-2 diabetes when used with metformin.
  - EMA CHMP Summary of opinion, 10 November 2016.

**Lonoctocog alfa for haemophilia A**
- **Product name**: Afstyla®
- **Dosage form**: Powder and solvent for solution for injection or infusion
- **Class**: Single-chain recombinant human factor VIII product; *ATC code*: B02BD02
- **Approval**: EMA CHMP recommendation
- **Use**: Treatment and prophylaxis of bleeding in patients with haemophilia A.
- **Benefits**: Ability to prevent and control bleeding when used on demand and when used for surgical procedures in adults and children with haemophilia A. Lonoctocog alfa has demonstrated a higher affinity for von Willebrand factor (VWF) than full-length recombinant factor VIII. VWF stabilises factor VIII and protects it from degradation.
  - EMA Summary of opinion, 10 November 2016.

**Etelcalcetide for secondary hyperparathyroidism**
- **Product name**: Parsabiv®
- **Dosage form**: Solution for injection
- **Class**: Synthetic peptide, calcimimetic agent 
  *ATC code*: H05BX04
- **Approval**: EMA
Use: Treatment of secondary hyperparathyroidism in adults with chronic kidney disease on haemodialysis therapy.
Benefits: Ability to reduce abnormally elevated serum parathyroid hormone levels in patients with chronic kidney disease on haemodialysis therapy.

EMA Summary of opinion, 15 September 2016.

Tenofovir alafenamide for chronic hepatitis B
Product name: Vemlidy®
Dosage form: Film-coated tablets
Class: Nucleotide reverse transcriptase inhibitor; ATC code: J05AF13
Approval: EMA
Use: Treatment of chronic hepatitis B in adults and adolescents aged 12 years and older.
Benefits: Ability to achieve a sustained antiviral response in treatment-naive and treatment-experienced patients.
Safety information: Lower impact on renal safety and bone mineral density compared to tenofovir disoproxil.

EMA CHMP Summary of opinion, 10 November 2016.

Olaratumab for soft tissue sarcoma
Product name: Lartruvo®
Dosage form: Concentrate for solution for infusion
Class: Human IgG1 monoclonal antibody and antagonist of platelet derived growth factor receptor-α (PDGFR-α) expressed on tumour and stromal cells; ATC code: L01XC27
Approval: EMA (orphan product, accelerated assessment; conditional marketing authorization); FDA (orphan drug; fast track designation, priority review, breakthrough therapy, accelerated assessment)
Use: In combination with doxorubicin, treatment of adults with soft tissue sarcoma.

Benefits: Improved survival.
Safety information: Olaratumab has some serious risks including infusion-related reactions and embryo-foetal harm.

EMA Press release, 16 September 2016.
FDA News release, 19 October 2016.

Palbociclib for breast cancer
Product name: Ibrance®
Dosage form: Hard capsules
Class: Inhibitor of cyclin-dependent kinases (CDK) 4 and 6; ATC code: L01XE33
Approval: EMA
Use: In combination with other medicines, treatment of hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.
Benefits: Improved progression-free survival.

EMA Press release, 16 September 2016.

Eteplirsen for Duchenne muscular dystrophy
Product name: Exondys 51®
Dosage form: Injection for intravenous use
Class: Antisense oligonucleotide; ATC code: M09AX06 (temporary code)
Approval: FDA (orphan medicinal product, fast track designation; accelerated approval under a rare paediatric disease priority review voucher)
Use: Treatment of patients with Duchenne muscular dystrophy with a confirmed mutation of the dystrophin gene amenable to exon 51 skipping.
Benefits: Dystrophin increase in skeletal muscle (surrogate endpoint).
Notes: The FDA has required a study to assess whether the product improves motor function.

FDA News release, 19 September 2016.

Baricitinib for rheumatoid arthritis
Product name: Olumiant®
Dosage form: Tablets
Class: Selective and reversible inhibitor of Janus kinase (JAK) 1 and 2; ATC code: L04AA37
Approval: EMA
Use: Treatment of active rheumatoid arthritis in adults who cannot be treated with other disease-modifying anti-rheumatic drugs.
Benefits: Reduces the symptoms of rheumatoid arthritis
EMA Press release, 16 Dec 2016.

Naloxone nasal spray for opioid overdose
Product name: Narcan®
Dosage form: Nasal spray
Class: Antidote; ATC code: V03AB15
Approval: Health Canada (expedited review)
Use: Emergency treatment of opioid overdose (non-prescription use)
Notes: Since early 2016, naloxone is available without a prescription in Canada for emergency treatment of opioid overdose. A temporary import permit for a U.S. FDA-approved product was granted in July 2016.

Edotreotide for diagnosis of gastro-entero-pancreatic neuroendocrine tumours
Product name: SomaKit TOC®
Dosage form: Kit for radiopharmaceutical preparation
Class: Diagnostic radiopharmaceutical for tumour detection; ATC code: V09IX09
Approval: EMA (orphan product)
Use: After radiolabelling with gallium (68Ga) chloride solution, for Positron Emission Tomography (PET) imaging of somatostatin receptor overexpression in adult patients with well-differentiated gastro-entero-pancreatic neuroendocrine tumours.
Benefits: Ability to localize primary tumours and their metastases.
► EMA Summary of opinion, 13 October 2016.
Safety information: Boxed Warning about an increased risk of serious infections, lymphoma and other malignancies, including some fatal ones, in children and adolescent patients treated with tumour necrosis factor blockers, including adalimumab products.


Extension of indications

Empagliflozin to reduce cardiovascular risk in diabetes

Product name: Jardiance®
Approval: FDA
Newly approved use: To reduce the risk of cardiovascular death in adults with type 2 diabetes.
Notes: Empagliflozin is not intended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. It is contraindicated in patients with a history of serious hypersensitivity reactions to the medicine, severe renal impairment, end-stage renal disease, or those on dialysis.

FDA News release, 2 December 2016.

Maravirocin for use in children

Product name: Selzentry®
Approval: FDA
Newly approved use: For the treatment of CCR5-tropic human immunodeficiency virus type 1 (HIV 1) infection in patients 2 years of age and older weighing at least 10 kg.
Note: Maravirocin is not recommended in patients with dual/mixed- or CXCR4-tropic HIV-1.


Canakinumab for rare and serious auto-inflammatory diseases

Product name: Ilaris®
Approval: FDA
Newly approved use: Treatment of Tumour Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS); Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD); and Familial Mediterranean Fever (FMF) in adults and children.
Note: Canakinumab was previously FDA-approved for another periodic fever syndrome called Cryopyrin-Associated Periodic Syndromes (CAPS) and for active systemic juvenile idiopathic arthritis.


Nivolumab for Hodgkin’s lymphoma

Product name: Opdivo®
Approval: EMA
Publications and events

### Revised CIOMS ethical guidelines

**Geneva** – The Council for International Organizations of Medical Sciences (CIOMS) has released its revised *International Ethical Guidelines for Health-Related Research Involving Humans* (1). The Guidelines were written in close collaboration with WHO. They aim to indicate how the ethical principles for research involving humans – as set forth in the Declaration of Helsinki – can be effectively implemented, particularly in low- and middle-income countries.

The scope of the Guidelines has been broadened to include research on health-related data. The revised Guidelines place more emphasis on the scientific and social value of research to ensure that important unsolved questions are addressed, and on the context in which research is conducted. They recognize that low resource settings may exist in high- and middle-income countries. They further call for governance systems to protect the interests of individuals in a world where informed consent is proving inappropriate for the growing number of health-related studies.

A commentary on the revised Guidelines has been published in *JAMA* (2).


### Access to medicines

**UN High Level Panel report on access to health technologies**

**New York** – The United Nations High Level Panel on access to medicines has published a groundbreaking new report, stating that the world must take bold new approaches to health technology innovation and ensuring access so that all people can benefit from the medical advances that have dramatically improved the lives of millions around the world in the last century.

The Panel suggested that initially governments should begin negotiating a code of principles for biomedical research and development (R&D) and report annually on their progress, in preparation for negotiating a binding convention that de-links the costs of R&D from end prices. The Panel noted with grave concern reports of governments being subjected to undue political and economic pressure to forgo the use of the flexibilities provided in the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), and felt strongly that this was undermining their efforts to meet their human rights and public health obligations. The Panel views transparency as a core component of accountability frameworks to hold all stakeholders responsible for the impact of their actions on innovation and access.

The High Level Panel was established by the United Nations Secretary-General to propose solutions for addressing the incoherences between international human rights, trade, intellectual property
rights and public health objectives. Humanitarian organizations have welcomed the report, urging governments and the international community to implement its recommendations.


Report of the Lancet Commission on Essential Medicines

London – The Lancet Commission on Essential Medicines has presented its report. The Commission was established in late 2014 to take stock of progress and challenges in providing access to affordable and quality-assured essential medicines for all. Thirty years after the first international conference on essential medicines policies, held in 1985 in Nairobi, the report provides recommendations to implement effective essential medicines policies in five crucial areas.

• Paying for a basket of essential medicines: An estimated US$ 13–25 per person per year is required to finance a basic package of 201 essential medicines. Yet in 2010, the majority of low-income countries and 13 of 47 middle-income countries spent less than US$ 13 per capita on pharmaceuticals.

• Making essential medicines affordable. National and global policies – such as promoting the use of generic medicines, price transparency and pooled procurement – can support sustainable access to essential medicines if they are implemented effectively. Related to this, the Commission warns that flexibilities included in the World Trade Organisation’s Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS), which provide governments with options that allow for the protection of public health, are under continual threat from the TRIPS-plus obligations included in bilateral and regional trade agreements.

• Assuring the quality and safety of medicines. The Commission’s recommendations build on existing procurement strategies for certain donor-funded medicines and on emerging trends towards regulatory collaboration and electronic communications. They call for the use of an international standard regulatory dossier with a harmonized content and format, and for a moving focus of WHO Prequalification on new essential medicines. Recommendations are also made on good practices in procurement and regulation, with concrete targets and a public accountability mechanism for the performance of regulatory authorities.

• Promoting the appropriate use of essential medicines. The Commission’s recommendations focus on strategies that enable collaboration among patients, health-care providers, insurers, supply chain managers, and others – including the pharmaceutical industry – to incentivize and support quality medicines use. The authors say that a key driver of inappropriate medicines use is pharmaceutical promotion, which should be controlled and monitored by robust regulatory authorities.

• Global research and development (R&D) framework. The Commission recommends that the costs of R&D should be delinked from the price of medicines and funded up-front from a Global Research Fund. Following the success of patent
pools for antiretrovirals and other medicines categories the report calls for the creation of a general essential medicines patent pool, to licence patents to other companies in order to create a competitive generics market. The Commission calls for strong government and international leadership to effectively implement essential medicines policies and create accountability, and proposes a set of 24 indicators to measure progress.

The work of the Commission was funded by the Bill & Melinda Gates Foundation, WHO, the University Medical Centre Groningen, Boston University, and by academic institutions and other organizations that allowed their staff to devote time to the work of the Commission.

► Press release, 7 November 2016.


Access to Medicine Index 2016


The Index ranks 20 of the world’s largest pharmaceutical companies on their efforts to improve access to medicine in low- and middle-income countries, identifies best practices and highlights progress and remaining gaps. The findings show that the pharmaceutical industry is extremely diverse. GSK leads the ranking for the fifth time, followed by Johnson & Johnson, Novartis and Merck KGaA.

Pharmaceutical companies have 850 products on the market for the 51 most burdensome diseases in low- and middle-income countries, and are developing another 420. Seven companies have published new or expanded pledges since 2014 to waive or abandon patent rights for certain products in certain regions, and new commitments are pointing the way to broader use of voluntary licensing in the future. However, middle-income countries outside of sub-Saharan Africa are more likely to be left out of licensing agreements. Also, companies apply for marketing authorization in only 25% of the countries that the Index identifies as highest priority.

The Index is published every two years by the Access to Medicine Foundation, an independent non-profit organisation funded by the UK Government (UK AID), the Dutch Ministry of Foreign Affairs and the Bill & Melinda Gates Foundation.


High price of hepatitis C treatment

Geneva – A new WHO report shows that over one million people in low- and middle-income countries have been treated with the new direct-acting antiviral medicines for hepatitis C since their introduction two years ago, despite the very high cost of these products. The report includes information on access, prices, patents and registration of hepatitis C medicines, supporting country efforts to increase access to these medicines.

Among middle-income countries, the prices of hepatitis C medicines vary greatly. For example, a three-month treatment with sofosbuvir and daclatasvir costs from US$ 9 400 in Brazil to US$ 79 900 in Romania. The report shows how political will, civil society advocacy and pricing negotiations are helping to
make treatment accessible for people who need it. Nevertheless, the high prices of hepatitis C treatments remain a major barrier to their access. WHO is working on new pricing models for these and other expensive medicines in order to increase access to all essential medicines in all countries.


Medicines patent and licences database upgraded

Geneva – The Medicines Patent Pool (MPP) has upgraded its patent database to include patent and licensing data for HIV, hepatitis C and tuberculosis medicines. The Medicines Patents & Licences Database (MedsPaL) includes data covering 4,000 national patent applications in more than 100 low- and middle-income countries (LMICs).

MedsPaL offers searchable information on 35 patented medicines and more than 100 pharmaceutical formulations for the treatment of HIV, hepatitis C and tuberculosis included in WHO guidelines or in its Essential Medicines List. The information is regularly updated through automatic data feeds from the European Patent Office’s public database Espacenet, online searches, expert analysis and collaboration with national patent offices.

► MPP Press release, 5 October 2016.

The Medicines Patents & Licences Database is available at: www.medspal.org

Updated paediatric ARV formulary and list

The Inter-Agency Task Team (IATT) on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children has published the 2016 update to the IATT Paediatric ARV Formulary and Limited-Use List. This edition reflects the 2016 WHO Consolidated Guidelines and takes account of changes in the markets. The formulary serves as guidance for treatment programmes, procurement agencies, funders and manufacturers to select optimal dosage forms for children.

► WHO/IATT/UNICEF. Policy brief. IATT paediatric ARV formulary and limited-use list: 2016 update.

Quality of medicines

Sample testing survey on medicines for women and children

Geneva – WHO has published a report of a quality testing survey of selected medicines from the list of 13 life-saving commodities as identified by the UN Commission on Life-Saving Commodities for Women and Children (UNCoLSC) (1). The survey was organized by the WHO Prequalification Team in cooperation with the national medicines regulatory authorities and Ministries of Health of Burkina Faso, Kenya, Madagascar, Nepal, Nigeria, Tajikistan, Tanzania, Uganda, Viet Nam and Zimbabwe. A total of 204 samples were collected and tested, of which 157 (77%) complied with the specifications set for the survey. Eleven samples of WHO-prequalified medicines were included in the survey, and all complied with specifications. A summary of the findings was published in an earlier issue of this journal (2).
The survey provides a snapshot of the quality of the sampled products and their availability in selected countries. The results enable WHO to confirm to which extent compliant testing results are supported by compliance with good manufacturing practice and proper regulatory documentation.


(2) Quality and availability of selected life-saving reproductive health medicines in developing countries. WHO Drug Information 2015;29(3):324-333.

Fighting poor-quality medicines in low- and middle-income countries

An article in the *Journal of Pharmaceutical Policy and Practice* highlights the divide in pharmaceutical quality between the North and the South. The authors warn that despite an increasing awareness of the problem and the launch of some positive initiatives the issue continues to expose patients in low- and middle-income countries to the risk of receiving poor-quality medicines. They call for more advocacy to achieve universal access to quality-assured medicines and emphasize that this advocacy should be based on evidence from research and monitoring programmes, should target all stakeholders – regulators, international organizations, journalists, purchasers, prescribers, programme managers, policy makers, public health actors and patients – and should be grounded in a common understanding of the technical concepts.


Prepare an overview of the Landmark UN declaration on antimicrobial resistance.

**Landmark UN declaration on antimicrobial resistance**

New York – For the first time, Heads of State have committed to taking a broad, coordinated approach to address the root causes of antimicrobial resistance across multiple sectors, especially human health, animal health and agriculture. The pledge was made at a high-level meeting on antimicrobial resistance convened by the President of the 71st session of the UN General Assembly. Countries reaffirmed their commitment to develop national action plans based on the “Global Action Plan on Antimicrobial Resistance” developed in 2015 by WHO in coordination with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE). They pledged to strengthen the regulation of antimicrobials, improve knowledge and awareness, promote best practices, and foster innovative approaches using alternatives to antimicrobials and new technologies for diagnosis and vaccines. (1)

This is only the fourth time a health issue has been taken up by the UN General Assembly. The other issues were HIV, non-communicable diseases and Ebola. In her opening speech, the WHO Director-General stressed that actions are urgently needed, and that a global crisis of this magnitude demands attention at the highest political level. The declaration was spearheaded by a campaign led by health officials from the United Kingdom (2)

(1) Office of the President of the UN General Assembly (OPGA)/WHO/FAO/OIE Joint news release. 21 September 2016.

The economic threat of drug-resistant infections

New York – The World Bank has released a new research report showing that by 2050, drug-resistant infections could cause global economic damage similar to that of the 2008 financial crisis. The impact of antimicrobial resistance would reduce annual global gross domestic product (GDP), pushing up to 28 million people into poverty by 2050. At the global level the volume of real exports would shrink, healthcare costs could increase by more than US$ 1 trillion per year, and economic losses could amount to an estimated US$ 100 trillion by 2050.

The report recommends a number of solutions to address the crisis. It highlights the need to strengthen investments in public and veterinary health systems and overall preparedness to tackle infectious diseases, with surveillance for antimicrobial resistance as an integral component. It strongly supports implementation and adequate financing of the WHO Action plan on Antimicrobial Resistance, which was endorsed in 2015.


Clinical use of medicines

Mentoring programme

Basle – The Clinical Division of International Union of Basic and Clinical Pharmacology (IUPHAR) has initiated a pilot programme to establish a list of “mentor departments” who are willing to provide advice in the area of clinical pharmacology, ranging from simple communication through to collaborative research and researcher exchange. Five centres – located in Scotland, Spain, South Korea, Australia and Canada – were listed at the time of writing. (1)

There is a pressing need to improve the use of medicines to maximize their effectiveness and minimize their harms. This can be best achieved by expanding knowledge and expertise of clinical pharmacology and therapeutics around the world. The mentoring centres will support, mentor or train future generations with skills to undertake research and teaching in this area and to serve on governmental organizations involved in medicines regulation and health technology assessment. The pilot programme is consistent with WHO initiatives such as the Essential Medicines List, and is in line with the joint IUPHAR/WHO publication Clinical Pharmacology in Health Care, Teaching and Research (2).

► (1) IUPHAR Clinical Divisions. Mentoring Centres [website].


Disease updates

Tuberculosis: WHO global report

Geneva, Washington – WHO has published its 2016 Global tuberculosis report. The report highlights the inequalities among countries with respect to access to medical products to fight tuberculosis, and signals the need for bold political commitment and increased funding.

In low- and middle-income countries, most of which continue to rely heavily on international donations, investments to curb the tuberculosis epidemic are almost US$ 2 billion short of the US$ 8.3 billion needed in 2016. In addition, WHO
estimates that at least US$ 1 billion per year is needed to accelerate the development of new vaccines, diagnostics, and medicines.

In 2015, there were an estimated 10.4 million new tuberculosis cases worldwide. Six countries accounted for 60% of the total burden. India has the most cases, followed by Indonesia, China, Nigeria, Pakistan and South Africa. An estimated 1.8 million people died from tuberculosis in 2015, of whom 0.4 million were co-infected with HIV. Although global deaths from tuberculosis fell by 22% between 2000 and 2015, the disease was among the top 10 causes of death worldwide in 2015, responsible for more deaths than HIV and malaria. Gaps in diagnosis and reporting remain major challenges. An estimated 480 000 people contracted multidrug-resistant tuberculosis in 2015, with India, China, and the Russian Federation together accounting for nearly half of all cases.


Measles: immunization gap persists

New York/Atlanta/Geneva – New data show that despite a 79% worldwide decrease in measles deaths between 2000 and 2015, the disease remains one of the leading causes of death among young children globally with an estimated 134 000 children having died from it in 2015.

Mass measles vaccination campaigns and a global increase in routine measles vaccination coverage saved an estimated 20.3 million young lives between 2000 and 2015, according to UNICEF, WHO, Gavi, the Vaccine Alliance, and the Centers for Disease Control and Prevention (CDC).

But progress has been uneven, and the target of the Global Vaccine Action Plan implementation to eliminate measles in four of six WHO regions by 2015 has been missed. The Democratic Republic of the Congo, Ethiopia, India, Indonesia, Nigeria and Pakistan accounted for half of the unvaccinated infants and 75% of the measles deaths in 2015. Large outbreaks were reported in Egypt, Ethiopia, Germany, Kyrgyzstan and Mongolia, and outbreaks were also reported in Nigeria, Somalia and South Sudan. In Germany and Mongolia older persons were affected, highlighting the need to vaccinate adolescents and young adults who have no protection against measles.


Malaria: funding secured for vaccine pilots

Geneva – Funding has been secured for the initial phase of pilot projects to roll out the world’s first malaria vaccine in sub-Saharan Africa. Vaccinations are due to begin in 2018. The Global Fund to Fight AIDS, Tuberculosis and Malaria has approved US$ 15 million covering the first phase of the pilot. Earlier in 2016, Gavi, the Vaccine Alliance had committed up to US$ 27.5 million and UNITAID had pledged US$ 9.6 million.

The vaccine, known as RTS,S, provides partial protection against P. falciparum malaria in young children. It was developed through a partnership between GlaxoSmithKline and the PATH
Malaria Vaccine Initiative (MVI), with support from the Bill & Melinda Gates Foundation and from a network of African research centres. In July 2015 the EMA issued a positive scientific opinion of the RTS,S vaccine, and in October 2015, two independent WHO advisory groups recommended its pilot implementation in 3–5 settings in sub-Saharan Africa.

The RTS,S vaccine is proposed as a tool to complement the current WHO-recommended malaria interventions. ►WHO News release, 17 November 2016.

Zika: end of public health emergency
The fifth meeting of the Emergency Committee (EC) on Zika and microcephaly was convened by the Director-General under the International Health Regulations (IHR 2005) on 18 November 2016. Research has now demonstrated the link between Zika virus infection and microcephaly, making it necessary to develop a robust longer-term mechanism to manage the global response.

The EC felt that, while Zika virus and associated consequences remain a significant public health challenge, they no longer represent a Public Health Emergency of International Concern (PHEIC). The EC recommended that a sustained programme of work should be established with dedicated resources to address the long-term nature of the disease and its associated consequences, and agreed to the proposed WHO Zika transition plan. Based on this advice, the Director-General declared the end of the PHEIC and reissued the Temporary Recommendations, which will be incorporated into the longer-term response mechanism. ►WHO Statement, 18 November 2016.

WHO matters

Model prequalification dossier
Geneva – The WHO Prequalification Team – medicines (PQTm) has published a model dossier on its website, illustrating how data should be submitted to WHO for prequalification. The model dossier is intended to serve as a training tool for regulators, as guidance for applicants, and as an example case for organizations involved in harmonizing regulatory requirements.

WHO requires that dossiers for generic medicines are submitted in the Common Technical Document (CTD) format of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The model dossier includes the completed quality templates and the corresponding data expected in CTD Module 3, with proprietary information redacted. ►PQ update, 14 September 2016.

Feedback is encouraged and should be sent to: Dr. M. Stahl, Group Leader Medicines Assessments, WHO Prequalification Team – Medicines; stahlm@who.int.

New medicines invited for prequalification
Geneva – WHO has published new invitations for Expression of Interest for prequalification (EOI). The 14th EOI for anti-TB medicines newly includes isoniazid/rifapentine 150mg/150mg dispersible tablets and 300mg/300mg coated tablets or capsules, as well as gatifloxacin 200mg tablets and 400 mg scored tablets. The 11th EOI for active pharmaceutical ingredients newly includes gatifloxacin. ►PQ Updates, 6 October and 7 October 2016.
Seminar for laboratories held in China
Shenzhen – The 5th WHO Interregional Seminar for Quality Control Laboratories involved in WHO Prequalification was held in Shenzhen, Guangdong Province, China in October 2016. It is the first time that this seminar was held in China. More than 60 laboratory directors from 42 countries and representatives from 26 provincial drug testing institutions of China participated in the technical discussions.
▶ China Food and Drug Administration (CFDA) News, 26 October 2016.

“Green” procurement of health commodities
Geneva - WHO has joined other international agencies in signing a Statement of Intent to align and “green” the procurement of health commodities, in an effort to protect the environment and contribute to sustainable development.

WHO and the other signatories – including GAVI, UNDP, UNICEF, the Global Fund, UNITAID, UNFPA and UNOPS – procure an estimated US$ 3 billion in health commodities each year. They have agreed to reflect their common commitment in their standard engagement with suppliers and manufacturers. They will also include it in their institutional strategies and policies.
▶ WHO News release, 7 December 2016.

New prequalification fee structure
Geneva – WHO, industry groups and key partners have agreed on a new fee structure that aims to support financial predictability, sustainability and expansion of prequalification services including the setting and public disclosure of quantitative performance targets.

The new arrangement is modelled on the practice of national regulatory authorities around the world, which charge application fees for evaluation and registration services. It will be launched in January 2017 for vaccines and medicines and in early 2018 for diagnostics.

WHO began to charge prequalification fees in 1999 for vaccines, in 2008 for diagnostics, and in 2013 for medicines. Before fees were introduced, the sole donor for vaccines prequalification was UNICEF, and medicines prequalification was funded by two donors, the Bill & Melinda Gates Foundation and UNITAID.

The new fee model is expected to generate revenues of about US$ 20 million annually, which will cover about half of the programme’s operating costs.
▶ PQ update, 30 September 2016.
WHO Prequalification Financing Model – Questions and Answers [website].

Upcoming events
2017 joint UNICEF-UNFPA-WHO manufacturers meeting
The 2017 joint UNICEF-UNFPA-WHO manufacturers meeting will take place in the week of 3 April 2017 in Copenhagen, Denmark. The manufacturers meeting provides information for suppliers of medical products for use by UN agencies and other international organizations.
▶ WHO Prequalification update, 30 September 2016.
ATC/DDD classification

The Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) as a measuring unit are tools for exchanging and comparing data on drug use at international, national or local levels. The ATC/DDD system has become the gold standard for international drug utilization research. It is maintained by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway. Visit www.whocc.no/ for more information.

ATC/DDD classification (temporary)

The following ATC codes and DDDs were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in October 2016. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology before 1 February 2017. If no objections are received before this date, the new ATC codes and DDDs will be considered final and included in the January 2018 version of the ATC/DDD Index.

New ATC 5th level codes

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>benralizumab</td>
<td>R03DX10</td>
</tr>
<tr>
<td>binimetinib</td>
<td>L01XE41</td>
</tr>
<tr>
<td>brigatinib</td>
<td>L01XE43</td>
</tr>
<tr>
<td>cerliponase alfa</td>
<td>A16AB17</td>
</tr>
<tr>
<td>dupilumab</td>
<td>D11AH05</td>
</tr>
<tr>
<td>eteplirsen</td>
<td>M09AX06</td>
</tr>
<tr>
<td>etirinotecan pegol</td>
<td>L01XX56</td>
</tr>
<tr>
<td>hydromorphone and naloxone</td>
<td>N02AA53</td>
</tr>
<tr>
<td>idursulfase beta</td>
<td>A16AB16</td>
</tr>
<tr>
<td>insulin glargine and lixisenatide</td>
<td>A10AE54</td>
</tr>
<tr>
<td>Lavandulae aetheroleum</td>
<td>N05BX05</td>
</tr>
<tr>
<td>lutetium (177Lu) oxodotreotide</td>
<td>V10XX04</td>
</tr>
<tr>
<td>mepyramine theophyllinacetate</td>
<td>R03DA12</td>
</tr>
<tr>
<td>migalastat</td>
<td>A16AX14</td>
</tr>
<tr>
<td>netarsudil</td>
<td>S01EX05</td>
</tr>
<tr>
<td>niraparib</td>
<td>L01XX54</td>
</tr>
<tr>
<td>obiltoxazimab</td>
<td>J06BB22</td>
</tr>
<tr>
<td>olaratumab</td>
<td>L01XC27</td>
</tr>
<tr>
<td>opicapone</td>
<td>N04BX04</td>
</tr>
<tr>
<td>ozenoxacin</td>
<td>D06AX14</td>
</tr>
<tr>
<td>padeliporfin</td>
<td>L01XD07</td>
</tr>
<tr>
<td>pegteogastim</td>
<td>L03AA17</td>
</tr>
<tr>
<td>plitidepsin</td>
<td>L01XX57</td>
</tr>
</tbody>
</table>

Continued
**New ATC 5th level codes (continued)**

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>ramipril, amlodipine and hydrochlorothiazide</td>
<td>C09BX03</td>
</tr>
<tr>
<td>rebamipide</td>
<td>A02BX14</td>
</tr>
<tr>
<td>ribociclib</td>
<td>L01XE42</td>
</tr>
<tr>
<td>romosozumab</td>
<td>M05BX06</td>
</tr>
<tr>
<td>rosuvastatin, amlodipine and perindopril</td>
<td>C10BX14</td>
</tr>
<tr>
<td>rosuvastatin, perindopril and indapamide</td>
<td>C10BX13</td>
</tr>
<tr>
<td>rucaparib</td>
<td>L01XX55</td>
</tr>
<tr>
<td>semaglutide</td>
<td>A10BJ06</td>
</tr>
<tr>
<td>sodium zirconium cyclosilicate</td>
<td>V03AE10</td>
</tr>
<tr>
<td>sofosbuvir and velpatasvir</td>
<td>J05AX69</td>
</tr>
<tr>
<td>suvorexant</td>
<td>N05CM19</td>
</tr>
<tr>
<td>tetracaine, combinations</td>
<td>N01BA53</td>
</tr>
<tr>
<td>velmanase alfa</td>
<td>A16AB15</td>
</tr>
<tr>
<td>zoster, purified antigen</td>
<td>J07BK03</td>
</tr>
</tbody>
</table>

1) Temporary code in J05AX69 will be changed to J05AP55 in connection with the implementation of the proposed new ATC 4th level *Antivirals for treatment of HCV infections* in 2018.

**New ATC level codes (other than 5th levels)**

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antivirals for treatment of HCV infections</td>
<td>J05AP</td>
</tr>
</tbody>
</table>

**Change of ATC codes**

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>Previous ATC</th>
<th>New ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>argipressin</td>
<td>H01BA06</td>
<td>H01BA01</td>
</tr>
<tr>
<td>asunaprevir</td>
<td>J05AE15</td>
<td>J05AP06</td>
</tr>
<tr>
<td>benzydamine</td>
<td>A01AD02</td>
<td>R02AX03</td>
</tr>
<tr>
<td>boceprevir</td>
<td>J05AE12</td>
<td>J05AP03</td>
</tr>
<tr>
<td>ceftriaxone, combinations</td>
<td>J01DD54</td>
<td>J01DD63</td>
</tr>
<tr>
<td>daclatasvir</td>
<td>J05AX14</td>
<td>J05AP07</td>
</tr>
<tr>
<td>dasabuvir</td>
<td>J05AX16</td>
<td>J05AP09</td>
</tr>
<tr>
<td>dasabuvir, ombitasvir, paritaprevir and ritonavir</td>
<td>J05AX66</td>
<td>J05AP52</td>
</tr>
<tr>
<td>elbasvir and grazoprevir</td>
<td>J05AX68</td>
<td>J05AP54</td>
</tr>
<tr>
<td>faldaprevir</td>
<td>J05AE13</td>
<td>J05AP04</td>
</tr>
<tr>
<td>ombitasvir, paritaprevir and ritonavir</td>
<td>J05AX67</td>
<td>J05AP53</td>
</tr>
<tr>
<td>ribavirin</td>
<td>J05AB04</td>
<td>J05AP01</td>
</tr>
<tr>
<td>simeprevir</td>
<td>J05AE14</td>
<td>J05AP05</td>
</tr>
<tr>
<td>sofosbuvir</td>
<td>J05AX15</td>
<td>J05AP08</td>
</tr>
<tr>
<td>sofosbuvir and ledipasvir</td>
<td>J05AX65</td>
<td>J05AP51</td>
</tr>
<tr>
<td>sofosbuvir and velpatasvir</td>
<td>J05AX69</td>
<td>J05AP55</td>
</tr>
<tr>
<td>telaprevir</td>
<td>J05AE11</td>
<td>J05AP02</td>
</tr>
</tbody>
</table>

1) Altered ATC level name to *vasopressin (argipressin)*
2) Split of code. Alteration of ATC code includes only benzydamine lozenges
3) Split of code. Combinations of ceftriaxone and other substances remain in J01DD54 while combinations of ceftriaxone and beta-lactamase inhibitors are moved to J01DD63
4) Temporary new code in J05AX69 will be changed to J05AP55 in connection with the implementation of the proposed new ATC 4th level *Antivirals for treatment of HCV infections* in 2018 (see temporary list “New ATC level codes (other than 5th levels)“
Temporary

Change of ATC level names

<table>
<thead>
<tr>
<th>Previous</th>
<th>New</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxicillin and enzyme inhibitor</td>
<td>amoxicillin and beta-lactamase inhibitor</td>
<td>J01CR02</td>
</tr>
<tr>
<td>ampicillin and enzyme inhibitor</td>
<td>ampicillin and beta-lactamase inhibitor</td>
<td>J01CR01</td>
</tr>
<tr>
<td>Bile acid preparations</td>
<td>Bile acids and derivatives</td>
<td>A05AA</td>
</tr>
<tr>
<td>cefoperazone, combinations</td>
<td>cefoperazone and beta-lactamase inhibitor</td>
<td>J01DD62</td>
</tr>
<tr>
<td>cefotaxime, combinations</td>
<td>cefotaxime and beta-lactamase inhibitor</td>
<td>J01DD51</td>
</tr>
<tr>
<td>ceftazidime, combinations</td>
<td>ceftazidime and beta-lactamase inhibitor</td>
<td>J01DD52</td>
</tr>
<tr>
<td>ceftolozane and enzyme inhibitor</td>
<td>ceftolozane and beta-lactamase inhibitor</td>
<td>J01DI54</td>
</tr>
<tr>
<td>imipenem and enzyme inhibitor</td>
<td>imipenem and cilastatin</td>
<td>J01DH51</td>
</tr>
<tr>
<td>piperacillin and enzyme inhibitor</td>
<td>piperacillin and beta-lactamase inhibitor</td>
<td>J01CR05</td>
</tr>
<tr>
<td>ticarcillin and enzyme inhibitor</td>
<td>ticarcillin and beta-lactamase inhibitor</td>
<td>J01CR03</td>
</tr>
</tbody>
</table>

New DDDs

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>DDD unit</th>
<th>Adm. R.*</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>rebamipide 0.3 g</td>
<td>O</td>
<td>A02BX14</td>
<td></td>
</tr>
<tr>
<td>voglibose 0.6 mg</td>
<td>O</td>
<td>A16BF03</td>
<td></td>
</tr>
<tr>
<td>migalastat 61.5 mg</td>
<td>O</td>
<td>A14AX14</td>
<td></td>
</tr>
<tr>
<td>vorapaxar 2.08 mg</td>
<td>O</td>
<td>B01AC26</td>
<td></td>
</tr>
<tr>
<td>selexipag 1.8 mg</td>
<td>O</td>
<td>B01AC27</td>
<td></td>
</tr>
<tr>
<td>ferric proteinsuccinylate 80 mg</td>
<td>O Fe+++</td>
<td>B03AB09</td>
<td></td>
</tr>
<tr>
<td>fimasartan 60 mg</td>
<td>O</td>
<td>C09CA10</td>
<td></td>
</tr>
<tr>
<td>ceftazidime and beta-lactamase inhibitor 6 g</td>
<td>P</td>
<td>J01DD52</td>
<td></td>
</tr>
<tr>
<td>pegteograstim 0.3 mg</td>
<td>P</td>
<td>L03AA17</td>
<td></td>
</tr>
<tr>
<td>opicapone 50 mg</td>
<td>O</td>
<td>N04BX04</td>
<td></td>
</tr>
<tr>
<td>pitolisant 18 mg</td>
<td>O</td>
<td>N07XX11</td>
<td></td>
</tr>
<tr>
<td>reslizumab 7.5 mg</td>
<td>P</td>
<td>R03DX08</td>
<td></td>
</tr>
<tr>
<td>doxylamine 25 mg</td>
<td>O</td>
<td>R06AA09</td>
<td></td>
</tr>
</tbody>
</table>

1) Previous level name, ceftazidime, combinations
2) Refers to ceftazidime

Changes of DDDs

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>Previous DDD DDD Unit</th>
<th>Previous DDD Adm. R.*</th>
<th>New DDD DDD Unit</th>
<th>New DDD Adm. R.*</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>daclizumab 0.35 g</td>
<td>P</td>
<td>L04AC01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) Course dose

WHO Collaborating Centre
Oslo, November 2016
ATC/DDD classification (final)

The following ATC codes, DDDs and alterations were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in March 2016. These are considered as final and will be included in the January 2017 version of the ATC/DDD Index.

New ATC 5th level codes
Please note that the list does not include new ATC codes established as a result of ATC alterations.

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin, acetylsalicylic acid and perindopril</td>
<td>C10BX12</td>
</tr>
<tr>
<td>baricitinib</td>
<td>L04AA37</td>
</tr>
<tr>
<td>bentazepam</td>
<td>N05BA24</td>
</tr>
<tr>
<td>Betulae cortex</td>
<td>D03AX13</td>
</tr>
<tr>
<td>bezlotoxumab</td>
<td>J06BB21</td>
</tr>
<tr>
<td>burosumab</td>
<td>M05BX05</td>
</tr>
<tr>
<td>cinotapride</td>
<td>A03FA08</td>
</tr>
<tr>
<td>fluciclovine ((^{18})F)</td>
<td>V09IX12</td>
</tr>
<tr>
<td>fluoroestradiol ((^{18})F)</td>
<td>V09IX11</td>
</tr>
<tr>
<td>formoterol and glycopyrronium bromide</td>
<td>R03AL07</td>
</tr>
<tr>
<td>hydroquinidine</td>
<td>C01BA13</td>
</tr>
<tr>
<td>methacetin ((^{13})C)</td>
<td>V04CE03</td>
</tr>
<tr>
<td>midostaurin</td>
<td>L01XE39</td>
</tr>
<tr>
<td>naloxone</td>
<td>A06AH04</td>
</tr>
<tr>
<td>ocrelizumab</td>
<td>L04AA36</td>
</tr>
<tr>
<td>olmutinib</td>
<td>L01XE40</td>
</tr>
<tr>
<td>patiromer calcium</td>
<td>V03AE09</td>
</tr>
<tr>
<td>piketoprofen</td>
<td>M02AA28</td>
</tr>
<tr>
<td>pimavanserin</td>
<td>N05AX17</td>
</tr>
<tr>
<td>rolapitant</td>
<td>A04AD14</td>
</tr>
<tr>
<td>sarilumab</td>
<td>L04AC14</td>
</tr>
<tr>
<td>solithromycin</td>
<td>J01FA16</td>
</tr>
<tr>
<td>tenofovir alafenamide</td>
<td>J05AF13</td>
</tr>
<tr>
<td>tramadol and other non-opioid analgesics</td>
<td>N02AJ15</td>
</tr>
<tr>
<td>uridine triacetate</td>
<td>A16AX13</td>
</tr>
<tr>
<td>venetoclax</td>
<td>L01XX52</td>
</tr>
<tr>
<td>vosaroxin</td>
<td>L01XX53</td>
</tr>
</tbody>
</table>

New DDDs

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>DDD</th>
<th>unit</th>
<th>Adm.R*</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>bentazepam</td>
<td>75</td>
<td>mg</td>
<td>O</td>
<td>N05BA24</td>
</tr>
<tr>
<td>brivaracetam</td>
<td>0.1</td>
<td>g</td>
<td>O,P</td>
<td>N03AX23</td>
</tr>
<tr>
<td>ceftolozane and enzyme inhibitor(^{1})</td>
<td>3</td>
<td>g</td>
<td>P</td>
<td>J01DI54</td>
</tr>
<tr>
<td>dalbavancin</td>
<td>1.5</td>
<td>g</td>
<td>P</td>
<td>J01XA04</td>
</tr>
<tr>
<td>doxofylline</td>
<td>0.8</td>
<td>g</td>
<td>O,P</td>
<td>R03DA11</td>
</tr>
</tbody>
</table>

Continued
### New DDDs (continued)

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>DDD</th>
<th>unit</th>
<th>Adm.R.*</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>evolocumab</td>
<td>10</td>
<td>mg</td>
<td>P</td>
<td>C10AX13</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>1.2</td>
<td>g</td>
<td>P</td>
<td>M01AE01</td>
</tr>
<tr>
<td>idebenone</td>
<td>0.9</td>
<td>g</td>
<td>O</td>
<td>N06BX13</td>
</tr>
<tr>
<td>isavuconazole</td>
<td>0.2</td>
<td>g</td>
<td>O,P</td>
<td>J02AC05</td>
</tr>
<tr>
<td>mepolizumab</td>
<td>3.6</td>
<td>mg</td>
<td>P</td>
<td>R03DX09(4)</td>
</tr>
<tr>
<td>posaconazole</td>
<td>0.3</td>
<td>g</td>
<td>P</td>
<td>J02AC04</td>
</tr>
<tr>
<td>sebelipase alfa</td>
<td>5</td>
<td>mg</td>
<td>P</td>
<td>A16AB14</td>
</tr>
<tr>
<td>tiopronin</td>
<td>0.8</td>
<td>g</td>
<td>O</td>
<td>G04BX16(5)</td>
</tr>
</tbody>
</table>

* Administration Route: O=oral; P=parenteral

1) ATC level name will be changed to *ceftolozane and beta-lactamase inhibitor* in the 2018 ATC/DDD index. See temporary list
2) Refers to ceftolozane
3) Course dose
4) ATC code changed from L04AC06, new code valid from January 2017
5) ATC code changed from R05CB12, new code valid from January 2017

### Changes of DDDs

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>Previous DDD</th>
<th>New DDD</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DDD</td>
<td>Unit</td>
<td>Adm.R.*</td>
</tr>
<tr>
<td>posaconazole</td>
<td>0.8</td>
<td>g</td>
<td>O</td>
</tr>
<tr>
<td>thiocytic acid</td>
<td>0.2</td>
<td>g</td>
<td>O,P</td>
</tr>
</tbody>
</table>

* Administration Route: O=oral; P=parenteral

---

WHO Collaborating Centre
Oslo, November 2016