

WHO Drug Information

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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)
HPRA	Health Products Regulatory Authority, Ireland (www.hpra.ie)
HSA	Health Sciences Authority, Singapore (www.hsa.gov.sg)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (www.ich.org)
IGDRP	International Generic Drug Regulators Programme (https://www.igdrp.com)
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)
Ph. Int	<i>The International Pharmacopoeia</i> (http://apps.who.int/phint/)
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
WHO	World Health Organization (www.who.int)
WHO EMP	WHO Essential medicines and health products (www.who.int/medicines/en/)
WHO PQT	WHO Prequalification team (https://extranet.who.int/prequal/)

Note:

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

Safety of medicines

Priming resource-limited countries for pharmacovigilance

“Project 3-S”: Smart Safety Surveillance for priority medical products

Access to medicines and vaccines in low- and middle-income countries (LMICs) has improved in the past two decades. However there has not been a proportionate improvement in pharmacovigilance infrastructure and activities to monitor adverse events and address safety issues. This is of particular concern as there is a sizeable pipeline of novel products to be introduced in LMICs. These products are developed in well-resourced settings, with baseline safety data that may not be entirely applicable to the population and context of target countries.

Safety monitoring of medicines is essential to protect people from harm. The lack of functional pharmacovigilance structures could become a barrier to the introduction of these products to some LMICs and could seriously undermine the treatment options available to patients. A new project proposes to strengthen pharmacovigilance capacity in LMICs and, in the long-term, establish end-to-end safety surveillance of products from their clinical development to the post-market stages. In its current phase the project focuses on selected medicines and vaccines that will be introduced in the next few years.

Safety monitoring of medicines

Although rigorous clinical trials are conducted during medicines development, a complete set of safety data only becomes known once a product has been on the market for a long time. Continued safety monitoring in real world settings, where medicines are used together with other products, among different patient populations and in patients with multiple illnesses, is therefore critically important.

At the global level, pharmacovigilance is conducted through the WHO Programme

for International Drug Monitoring. Data are collected in Vigibase, the WHO global pharmacovigilance database of adverse events. Set up nearly five decades ago, this database is managed and maintained by the WHO Collaborating Centre in Sweden, also known as the Uppsala Monitoring Centre (UMC). Participation by WHO Member States has increased steadily, and as of November 2017, Vigibase has received more than 16 million individual case safety reports from 127 countries worldwide. The Vigibase data comply with the highest

This article is based on information contributed by the WHO Safety and Vigilance (SAV) Team and the Bill & Melinda Gates Foundation, with Monika Zweygarth as editor.

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scientific and ethical standards – including those developed by WHO, the International Council of Harmonization (ICH) and Council for International Organizations of Medical Sciences (CIOMS) – and are analyzed using sophisticated statistical methods to detect signals of possible adverse effects that are not yet known.

However, the capacity for pharmacovigilance is unevenly distributed among WHO Member States. While mature regulatory authorities have the relevant infrastructure and capacity to monitor medicines safety in line with international standards, this is not the case in most LMICs.

Challenges in LMICs

Weak regulatory systems

Although pharmacovigilance programmes have been created in many resource-limited countries since the 1990s they remain understaffed, underfunded and often without strong legal or regulatory provisions.⁽¹⁾ Data from WHO and its

collaborating centres suggest that only about one third of sub-Saharan African countries meet the WHO-defined minimum pharmacovigilance requirements,⁽²⁾ and many lack a standardized data management system.

As there is limited enforcement and awareness of pharmacovigilance in LMICs, few reports are made by health care providers and patients, and most of them lack clinically important information that could support causality assessment. And on the part of industry there is often little emphasis on local risk management plans in developing markets, given the limited pharmacovigilance requirements.⁽³⁾

As a result of these weaknesses, there is substantial underreporting of suspected adverse events in LMICs, and very few regulatory decisions on medicines safety in LMICs are based on local data.⁽⁴⁾ These shortcomings are also reflected in the reports made to VigiBase: Sub-Saharan African countries contribute less than 1% of all individual case safety reports (ICSR).

Box 1: Project Triple-S — Core approaches



Pilot products: Adopt a stepwise approach with an initial pilot for three new products (two medicines and one vaccine)



Leverage available resources from partners: WHO International Drug Monitoring Programme, Global Vaccine Safety Initiative, Uppsala Monitoring Centre and other WHO collaborating centres, national pharmacovigilance centres and others



Industry partnership: Develop integrated plans that include key marketing authorization holders



Holistic country plan: Develop a holistic plan for pharmacovigilance as part of medicines regulation in the defined countries



Collaboration: Liaise with other ongoing initiatives, such as the African Medicines Regulatory Harmonization (AMRH) initiative



Progressive development: Build pharmacovigilance infrastructure progressively, moving from minimum to mid-range and advanced capacity.

Complex health care systems

In most resource-limited countries the public and private health care systems are complemented by donor-funded public health programmes to fight high-burden diseases such as HIV, tuberculosis and malaria, to address neglected diseases, or to increase immunization coverage. Medical products dispensed in these programmes often account for the majority of pharmaceuticals used in resource-limited settings. They are often approved through fast-track mechanisms and scaled up rapidly, despite little experience with their safety in target countries.

The pharmacovigilance needs in the treatment of specific diseases have provided an opportunity to introduce pharmacovigilance systems into additional resource-limited countries. Between 2000 and 2010 the number of sub-Saharan African countries with functional pharmacovigilance centres increased from less than 10 to well over 20. In addition, donors have been supporting projects to monitor the safety and safe use of medicines in their programmes. However, where such projects exist they tend to have limited objectives and do not necessarily collaborate with national pharmacovigilance centres.⁽⁵⁾

Product pipeline for LMICs

The gaps in pharmacovigilance are problematic because an increasing pipeline of novel products designed for introduction in LMICs. Some products are under development for use exclusively in LMICs to treat neglected diseases such as Ebola, dengue, malaria, schistosomiasis, leishmaniasis or human African trypanosomiasis. Others are intended to fight diseases that affect countries globally, such as multi-drug resistant

tuberculosis, hepatitis C infection or human papillomavirus. And yet others may need to be developed rapidly in response to emergencies, as happened with Ebola vaccines during the West Africa epidemic.

However, these products are mostly being developed in well-resourced settings that do not reflect the social, economic, epidemiological or health conditions of LMICs. As a result, limited baseline safety data are available at the time of their approval for use in LMICs, making safety monitoring critical.

Project 3-S

Smart safety surveillance

To support LMICs in the introduction of new products, the WHO Safety and Vigilance (SAV) Team has initiated a project to optimize post-marketing surveillance of priority medicines and vaccines in LMICs. The project will use a smart safety surveillance (“3-S”) approach that initially focuses on selected priority products to be introduced in LMICs. Regulators will be supported in identifying, assessing, and adequately managing the risks associated with these products. As safety data will be generated on specific products in parallel with their first use, national pharmacovigilance systems and competence will be strengthened to enable safety monitoring of all products in the long-term.

A new partnership between WHO and the Bill & Melinda Gates Foundation has been established to advance this work. Project 3-S proposes to strengthen, expand and streamline pharmacovigilance systems in LMICs. Its core approaches are designed to identify the strategies that work well, and scale them up to additional countries and products (*Box 1*).

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Pilot products

In its pilot phase Project 3-S will build surveillance systems for three pilot products. A shortlist of products has been drawn up taking into consideration emerging product launches, use of accelerated or conditional approval, adverse events identified in clinical development, public health impact, and exclusive target populations.

Project 3-S will be piloted in four to six countries of varying pharmacovigilance readiness. Surveys have been completed in 3 countries and are under way in another 4 to evaluate the successes and challenges in pharmacovigilance management. The pilot phase will serve to understand the types of countries and systems that will benefit the most from external support. If proven, the concept of Project 3-S will be extended to additional countries and regions.

Holistic country plan

Pharmacovigilance strengthening must be integrated with broader initiatives to strengthen regulatory systems. The ultimate goal of Project 3-S is to establish end-to-end pharmacovigilance systems, with timely and adequate reporting of adverse drug reactions, followed by timely review and any needed regulatory action. A holistic plan for pharmacovigilance will be developed in each country, covering: (1) policy, law and regulation, (2) system, structure and stakeholder coordination, (3) signal generation and data management, (4) risk assessment and evaluation, and (5) risk management, communication and allocation of commensurate resources.

Leverage available resources

To ensure effective safety monitoring in line with international standards, use will be made of guidance, infrastructure,

expertise and resources available from global partners (*Box 1*).

The importance of good alignment between medicines and vaccines vigilance is well recognized within Project 3-S. The new CIOMS Guide to Active Vaccine Safety Surveillance (6) provides valuable best practice guidance for developing pharmacovigilance and aligning the principles for vaccines and medicines. The two relevant WHO-convened global advisory committees will be represented in the Project Advisory Group and will provide advice on research protocols, methodologies, review data, and guide national investments and initiatives. The WHO public health programmes and the Prequalification Team can support the assessment of baseline product safety data in collaboration with regulators and industry.

To prepare the ground for Project 3-S, a core curriculum has been developed to train health professionals in quality reporting and analysis of adverse events in resource-limited settings. An inaugural training workshop took place in Mombasa, Kenya, in Q4 2016; representatives from 12 African countries attended. Training workshops of this nature will take place regularly going forward.

Progressive development

The project's success will depend on the target countries' ability to adopt and implement pharmacovigilance. An assessment of the potential target countries, and of relevant local stakeholders will be critical. WHO has coordinated the development of an up-to-date global set of indicators to assess pharmacovigilance readiness within the context of Project 3-S. These indicators are drawn from the 2015 WHO pharmacovigilance indicators (7) and other recognized global pharmacovigilance

and assessment tools. They will be used to assess the pharmacovigilance infrastructure, competence, capacity and gaps in target countries against global standards. As the project progresses, pharmacovigilance infrastructure will be expanded to build more advanced safety monitoring and risk minimization functions into the national regulatory systems. In this phase the CIOMS Working Group IX report *Practical Approaches to Risk Minimisation for Medicinal Products* (8) provides real life examples and can serve as a practical risk management toolkit.

Collaboration

An increasing number of organizations have become involved in regulatory systems strengthening. WHO is in the process of establishing a “Coalition of Interested Partners” framework to achieve better coordination, efficiency, outcomes and sustainability of the different partners’ efforts in Member States or regions.¹

Project 3-S will serve as a pathfinder pilot for this approach in the area of pharmacovigilance. Work-sharing and joint activities in ongoing initiatives such as the African Medicines Regulatory Harmonization (AMRH) and the African Vaccines Regulatory Forum (AVAREF) could create significant synergy and enhance impact. For example, a product could be monitored intensively in one or two countries and the data made available to neighbouring countries, or regional risk-assessment committees could jointly review data on priority products for mutual learning and regional decisions.

¹ The approach was endorsed in the 17th International Conference of Drug Regulatory Authorities (ICDRA) recommendation to “*Incorporate an innovative and more coordinated approach to regulatory systems strengthening such as coalition of interested partners and centres of excellence*”.(9)

To sustain the impact of Project 3-S beyond the pilot WHO has engaged with external partners who can provide technical expertise, financial investment or coordination capabilities. Key stakeholder meetings were held in October 2015, March 2016 and January 2017 to introduce the initiative, gain endorsement of the core objectives and approach, and ensure alliances are formed going forward. Major organizations have expressed their commitment to support Project 3-S, and the ongoing and planned contributions of each partner in different areas have been mapped.

Conclusion

There is growing international attention to strengthening pharmacovigilance globally. Members of the WHO advisory committee on safety of medicinal products have commented that Project 3-S with its focus on priority products will be a “game-changer” which may well impact future product launches.(3)

Encouragingly, there are examples of national systems that are stepping up to the need for safety monitoring of new medicines. In India a detailed procedure has been established for recording and reporting adverse events observed with bedaquiline at designated treatment sites for multidrug-resistant tuberculosis, and data are transferred automatically between the tuberculosis programme and the national pharmacovigilance database.(3)

The pharmacovigilance structures that now exist in some LMICs, and the strong interest that these countries demonstrate in improving their systems and capacity, could facilitate the success of Project 3-S both nationally and in collaborative or regional settings.

It is hoped that by involving the relevant national authority, and through

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integration in the national medicines policy, pharmacovigilance will become the norm for medical products in LMICs as part of each authority's regulatory mandate. Uptake and application of the key principles for strengthening pharmacovigilance systems in additional regions will be an important measure of success. Ultimately, such systems should enable regulators to respond quickly and adequately to potential safety risks with all products throughout their life cycle, ensuring that patients can rely on their health services to provide them with safe vaccines and medicines.

References

- 1 Olsson S, Pal SN, Dodoo A. Pharmacovigilance in resource-limited countries. *Expert Review of Clinical Pharmacology* 2015; 8:4, 449-460. DOI: [10.1586/17512433.2015.1053391](https://doi.org/10.1586/17512433.2015.1053391).
- 2 WHO Minimum Requirements for a Functional Pharmacovigilance System. 2010.
- 3 Fourteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP). 25-26 April 2017, WHO, Geneva [Feature]. *WHO Pharmaceuticals Newsletter* No. 4, 2017; pp. 26-32.
- 4 Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance activities in 55 low- and middle-income countries: a questionnaire-based analysis. *Drug Saf.* 2010 Aug 1;33(8):689-703.
- 5 Pal S, Dodoo A, Mantel A, Olsson S. *Pharmacovigilance and Safety of Medicines*. In: *The World Medicines Situation 2011*. Geneva: World Health Organization; 2011.
- 6 CIOMS. *Guide to Active Vaccine Safety Surveillance*. Report of CIOMS Working Group on Vaccine Safety. Geneva: Council for International Organizations of Medical Sciences (CIOMS); 2017. Available at: www.cioms.ch/shop.
- 7 2015 WHO Pharmacovigilance indicators.
- 8 CIOMS. *Practical Approaches to Risk Minimisation for Medicinal Products: Report of CIOMS Working Group IX*. 2014. Available at: www.cioms.ch/shop.
- 9 17th International Conference of Drug Regulatory Authorities. Cape Town, South Africa, 29 November–2 December 2016. *Recommendations*.

Further reading:

Marie-Paule Kieny and Trevor Mundel. *Putting Health and Safety First*. Huffington Post Contributor platform, 4 April 2017. 

Naming of medicines

Survey about International Nonproprietary Names (INN)

Level of familiarity with the INN nomenclature system among students, academics, scientists and healthcare practitioners

WHO assigns International Nonproprietary Names (INN) to pharmaceutical substances. A recent survey among health sciences students and professionals showed that not all respondents were equally aware of what INN are and how they are constructed. The findings of the survey will support efforts to promote the use of INN in practice. Furthermore, more knowledge about INN could enhance students' understanding of the different classes and modes of action of medicines.

Introduction

The INN nomenclature system provides unique identifications for pharmaceutical substances. The INN are constructed with a prefix and a stem, occasionally an infix is included where necessary. The stem in the INN gives an indication to the mode of action or pharmacological class of the substance being named. In addition each stem is developed with a definition that describes the agonistic, antagonistic, modulating or inhibitory property of the ligand.

The use of INN in the education of pharmacology and therapeutics is an excellent way to facilitate learning and help

students to recognize the classes of drugs and their modes of action. But are academics and students familiar with the INN nomenclature system? For that matter, are scientists and healthcare practitioners aware of how INN are constructed? In March 2016 the INN Programme of the World Health Organization (WHO) conducted a survey to evaluate a sample of participants on how familiar they are with the INN nomenclature system. The purpose of the study was to obtain an overview of the use of INN in practice and education around the world, and to identify gaps with a view to develop a strategic plan to promote the use of INN in practice and education.

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Survey about International Nonproprietary Names

Method

A brief online survey was designed comprising ten statements related to the familiarization and usage of INN. Participants were invited to respond to each statement on a 5-point Likert Scale (Strongly disagree / Disagree / Somewhat disagree, somewhat agree / Agree / Strongly agree), and there was also an “I do not know” option.

The following institutions and organizations were selected for recruitment of survey participants: universities, the user community of the WHO MedNet platform for INN¹, La Revue Prescrire², the International

Pharmaceutical Federation (FIP)³ and the International Union of Basic and Clinical Pharmacology (IUPHAR)⁴.

The survey questions were available in both English and French. Participants were requested to answer a single set of the questions offered in either language. The survey was open for one month during March 2016. Thereafter the data were collated and analyzed.

Respondents

A total of 1 074 respondents from 68 countries participated in the survey (*Table 1*), including 432 (40%) men and 642 (60%) women. The majority of

¹ <http://mednet.who.int> – password required

² French: <http://www.prescrire.org/fr/Summary.aspx>;
English: <http://english.prescrire.org/en/Summary.aspx>

³ <http://www.fip.org/>

⁴ <http://www.iuphar.org/>

Respondents' characteristics**Table 1: Countries of residence**

Country	English response	French response	Total
South Africa	65	1	66
Singapore	57		57
Italy	46	1	47
USA	33		33
Spain	23	2	25
France	20	633	653
Germany	20		20
Switzerland	18		18
United Kingdom	17		17
China	10		10
Japan	10		10
Others*	116	2	118
Total	435	639	1 074
	40.5%	59.5%	100%

Table 2: Occupation

Occupation	Number (%)
Students (including 47% pharmacy students and 21% medical students)	652 (61%)
Professionals	
Pharmacists	117 (11%)
Physicians	43 (4%)
Scientists/researchers (excluding professors)	72 (7%)
Academics (professors)	67 (6%)
Other professionals	123 (11%)
Total	1 074 (100%)

Table 3: Age (years)

	English	French	All
Range	19–76	16–72	16–76
Mode	22	18	18
Average	40.5	24.7	31.1

* *Table 1*, Others: (*Responses in English*) – Canada, Croatia, Australia, India, Russian Federation, Finland, Ireland, New Zealand, Peru, Portugal, Brazil, Costa Rica, Netherlands, Norway, Austria, Belgium, Chile, Colombia, Czech Republic, Denmark, Iceland, Malta, Mexico, Nigeria, Poland, Republic of Serbia, Sweden, Argentina, Bangladesh, Bulgaria, Cote d'Ivoire, Cuba, El Salvador, Hungary, Indonesia, Kenya, Kyrgyzstan, Latvia, Libyan Arab Jamahiriya, Malawi, Malaysia, Mongolia, Namibia, Philippines, Qatar, Republic of Korea, Romania, Rwanda, Saudi Arabia, Slovenia, Thailand, Turkey, Uganda, Uruguay, Venezuela, Vietnam. (*Responses in French*) – Algeria.

Survey about International Nonproprietary Names

the respondents were students and the remainder were professionals (*Table 2*). The students were mostly enrolled in life sciences courses, 44% of them were first-year students. The working experience of the professionals ranged from 1 to 50 years. The mean age of the respondents was 31 years; the participants who responded in French were younger on average than those who responded in English (*Table 3*).

Summary of results

An overview of results is provided in *Figure 1*. For the purpose of the summaries shown below, responses of “Agree” and “Strongly agree” were added together, as were responses of “Disagree” and “Strongly disagree”.

The examples given in the footnotes are included in this article for illustration, but were not provided in the survey.

1. Acronym

Eighty-five percent of all respondents knew that the acronym INN stands for International Nonproprietary Names; 7% answered that they did not know, and the remaining 8% thought that this was not the case.

2. INN versus generic names

Sixty-five percent of the respondents agreed that the INN of a medicine is the same as the generic name, 25% disagreed, and 11% did not know.

3. INN versus brand names

Almost three quarters (74%) of all respondents agreed that different manufacturers may give their products different trade names although the active ingredient has the same INN. Those in

agreement included 69% of the students and 81% of the professionals, indicating that the latter are more familiar with this situation. Thirteen percent disagreed with the statement, while 9% answered that they did not know.

4. INN stems

Seventy-one percent of all respondents (68% of the professionals and 73% of the students) agreed that pharmaceutical substances belonging to the same therapeutic or chemical class share the same stem in their INN.⁵ Only 6% of the respondents disagreed, but 14% of all respondents answered that they did not know, meaning that in total 20% of respondents were unaware of the function of INN stems and the remaining 9% were unsure (“Somewhat disagree, somewhat agree”).

5. “-mab” stem

Three quarters (76%) of the participants were aware that the “-mab” suffix in an INN designates a substance belonging to the class of immunological agents known as monoclonal antibodies,⁶ whereas 17% (19% of the students and 16% of the professionals) responded that they did not know and the remaining 7% disagreed wholly or partially with this statement.

6. How INN are assigned

Sixty-seven percent of the respondents were aware that WHO in collaboration with INN experts and national nomenclature committees assigns INN, while 25% of the participants (28% of the students and 21% of the professionals) did not know, and the others disagreed or partly disagreed.

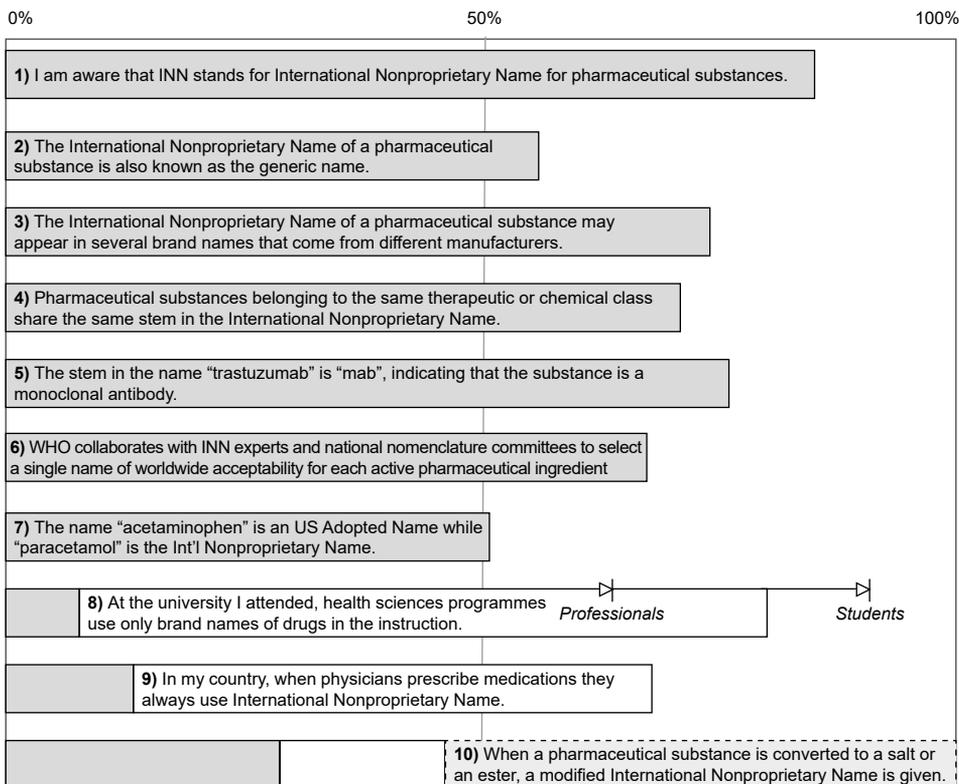
⁵ Example : the stem « -conazole » denotes triazole- or imidazole systemic antifungal agents: miconazole, ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole.(1)

⁶ Examples: rituximab, trastuzumab, gemtuzumab.(2)

Survey about International Nonproprietary Names

Figure 1: Overview of survey statements and responses (n = 1 074)

Majority response: Agree or strongly agree Disagree or strongly disagree Agree/disagree, or don't know

**7. Acetaminophen, paracetamol**

Just over half (51%) of all respondents, including 71% of the professionals and 38% of the students, agreed that acetaminophen is an US Adopted Name (USAN) while paracetamol is the INN of the same medicine. This leaves a surprisingly high proportion (29%) of professional respondents who were not aware that this very common medicine has two names.

8. Use of INN in teaching

Seventy-two percent of all respondents disagreed with the statement that at the

universities where they studied, the health sciences programmes use only brand names in teaching. This suggests that health science students across various countries may learn about medicines using INN or names commonly used in their continent, such as USAN, British approved names (BAN), other nationally approved non-brand names.

Interestingly, 83% of the students but only 56% of the professionals answered that brand names are not the only medicine names they learned during their courses. This suggests that the use of non-brand names in tertiary education has increased.

Survey about International Nonproprietary Names

This is indeed encouraging; however, the learning may be further enhanced if students learn more about the rules and principles according to which INN are constructed.

9. Use of INN in prescribing

Fifty-five percent of all respondents disagreed that physicians always use INN when prescribing medicines. Only 13% agreed, 25% somewhat agreed and somewhat disagreed, and 7% said they didn't know. The wording of the statement ("... always use INN...") may have discouraged some respondents from agreeing. Nevertheless this is an interesting finding: the responses to the previous question indicated that students learn about medicines using not only brand names, and yet in practice the use of brand names still appears to be prevalent.

10. Modified INN

Only 29% agreed to the statement that a salt or ester of a pharmaceutical substance is given a modified INN,⁷ 8% somewhat agreed and somewhat disagreed. Close to half (46%) of all respondents answered that they did not know, and 17% disagreed, adding up to 63% of all respondents (54% among professionals and 69% among students) who were not aware that INN are modified to designate a salt or ester form of a medicine.

Conclusions and recommendations

The survey was taken by a cross-section of professionals and students. The majority of the respondents were students, accounting for 61% of all participants.

It was found that students and professionals responded differently to most of the statements. This is not unexpected, as it can be assumed that professionals

are more experienced and may be better informed about the nomenclature of medicines than students. However, the responses suggest that professionals are still not familiar with certain aspects of the INN nomenclature system.

Generally, the respondents knew about the INN for pharmaceutical substances; however, they were less familiar with certain specific aspects, such as how INN are constructed and what the components in a name mean. This is not unexpected as most of the respondents were students, who may have had limited exposure to the concept of INN. The survey responses further suggested that although INN (or generic names) are increasingly used in teaching, in practice many physicians still prefer to prescribe using brand names.

Based on the survey findings it is recommended that practitioners should be encouraged to use INN for prescription and dispensing to harmonize medicine names around the world. It is further recommended that the principles of how INN are constructed and assigned should be more widely included in tertiary education. This would make learning about medicines more meaningful and less of rote learning, and would facilitate a better understanding of certain aspects of pharmacology.

References

- 1 WHO. [The use of stems in the selection of International Nonproprietary Names \(INN\) for pharmaceutical substances](#). WHO/EMP/RHT/TSN/2013.1. Geneva: World Health Organization; 2013.
- 2 WHO. [Revised monoclonal antibody \(mAb\) nomenclature scheme](#). Geneva, 26 May 2017.
- 3 WHO. [International Nonproprietary Names Modified](#). INN Working Document 05.167/3.

⁷ Example: The INN "clindamycin phosphate" denotes the phosphate salt form of clindamycin.(3)

Safety news

Safety warnings

Miconazole oral gel:

Do not use in patients taking warfarin

United Kingdom – The MHRA has warned that patients taking warfarin should not use over-the-counter miconazole oral antifungal gel. This follows reports of bleeding events, some with fatal outcome, in such patients. If miconazole oral gel must be used with an oral anticoagulant such as warfarin, patients should be monitored carefully, and the anticoagulant effect titrated carefully. Patients who experience sudden unexplained bruising, nosebleeds or blood in the urine should stop using miconazole and seek immediate medical attention.

A contraindication, and more prominent warnings about this risk, will be included in the product information and on the packaging for miconazole oral gel.

► [MHRA Drug Safety Update volume 11 issue 2, September 2017: 1.](#)

Obeticholic acid:

Serious liver injury

United States of America – The FDA has warned that obeticholic acid (Ocaliva®) is being dosed incorrectly in some patients with moderate to severe decreases in liver function, resulting in an increased risk of serious liver injury and death. Obeticholic acid may also be associated with liver injury in some patients with mild disease who are receiving the correct dose.

Patient's baseline liver function should be determined before treatment is initiated. Patients with moderate to severe liver

impairment (Child-Pugh B and C) should receive a dose of 5 mg once weekly, which can be increased up to a maximum of 10 mg twice weekly if needed. All patients treated with obeticholic acid should be monitored frequently, and the dosing frequency reduced to once- or twice-weekly for patients who progress to moderate or severe liver impairment. If liver injury is suspected, obeticholic acid should be stopped, and should only be started again after the patient has stabilized and if the benefits outweigh the risks. Patients should be educated on the symptoms of potential liver injury.

Obeticholic acid is used to treat primary biliary cholangitis, a rare, chronic disease that causes the bile ducts in the liver to become inflamed and destroyed, resulting in a build-up of bile in the liver which eventually loses its ability to function.

► [FDA Drug Safety Communication, 25 September 2017.](#)

Linagliptine:

Interstitial pneumonia

Japan – The PMDA has recommended that the product information for the antidiabetic medicine linagliptine should be updated to reflect the risk of interstitial pneumonia.

This follows reports of this adverse event observed in patients treated with linagliptin in Japan. The revised product information states that if signs and symptoms such as cough, dyspnoea, fever and abnormal chest sounds are observed, chest X-ray, chest CT scan and serum marker tests should be performed immediately. If interstitial pneumonia is suspected, the medicine

should be discontinued and appropriate measures taken, including administration of corticosteroids.

- ▶ [PMDA Summary of investigation results and MHLW Revision of precautions](#), 17 October 2017.

Dabigatran: **Liver toxicity**

Japan – The PMDA has informed health professionals that cases of acute liver failure, liver function disorder and jaundice have been reported in patients treated with the antithrombotic medicine dabigatran (Pradaxa®) in Japan. The MHLW has recommended to add a warning to the product information, stating that patients should be monitored, and in case of abnormalities dabigatran should be stopped and appropriate measures taken.

- ▶ [PMDA Summary of investigation results and MHLW Revision of precautions](#), 12 September 2017.

Flucloxacillin: **Metabolic acidosis**

Ireland – The HPRA has informed healthcare professionals that flucloxacillin, when used together with paracetamol, has been associated with very rare cases of high anion gap metabolic acidosis (HAGMA). Patients with severe renal impairment, sepsis or malnutrition might be at higher risk of this adverse event, especially if they are taking the maximum daily doses of paracetamol.

The warning follows a review by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), which advised that the product information should be updated to reflect this risk.

- ▶ [HPRA Drug Safety Newsletter, 83rd Edition](#), November 2017.

Epoetins: **Severe skin reactions**

Ireland – The Marketing Authorisation Holders (MAHs) of all epoetins available in Ireland, in agreement with EMA and HPRA, have warned health professionals that severe skin reactions, including some fatal ones, have been reported with epoetins in the post-marketing setting.

A detailed analysis of all available information revealed that severe skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can be considered to be a class effect of epoetins. More severe reactions were reported with long-acting epoetins. The frequency of these reactions could not be calculated, but they appear to occur very rarely.

Patients should be instructed to contact their doctor immediately and stop epoetin treatment if they experience any signs or symptoms of a severe skin reaction. Patients who have developed such reactions due to the use of an epoetin must never be given an epoetin again.

The product information of all epoetin-containing products is being updated to reflect these warnings.

- ▶ [HPRA. Direct Healthcare Professional Communication](#), September 2017.

Intraocular vancomycin: **Potentially blinding complications**

United States of America – Many ophthalmologists use intraocular vancomycin during cataract surgery to prevent postoperative endophthalmitis. The FDA has informed health professionals that haemorrhagic occlusive retinal vasculitis (HORV) has been observed in dozens of patients after injections of vancomycin into the eye at the end of

otherwise uncomplicated cataract surgeries. HORV is a newly described, rare, potentially blinding postoperative complication.

The FDA has recommended against the prophylactic use of intraocular vancomycin, alone or with other active ingredients, during cataract surgery.

There is no FDA-approved intraocular vancomycin formulation. The injection is usually prepared on site or obtained from a compounding pharmacy. A warning has been added to the product information of vancomycin injection, stating that the safety and efficacy of vancomycin administered by the intracameral or the intravitreal route have not been established, and that vancomycin is not indicated for prophylaxis of endophthalmitis.

- ▶ FDA. [A Case of Hemorrhagic Occlusive Retinal Vasculitis \(HORV\) Following Intraocular Injections of a Compounded Triamcinolone, Moxifloxacin, and Vancomycin Formulation.](#) 3 October 2017.

Fingolimod: **Contraindicated in patients with heart conditions**

Ireland – The marketing authorization holder, in agreement with EMA and HPRA, has informed healthcare professionals that fingolimod is now contraindicated in patients with myocardial infarction, unstable angina pectoris, stroke, transient ischaemic attacks, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure in the previous 6 months. It is also contraindicated in patients with severe cardiac arrhythmias requiring treatment with certain anti-arrhythmic drugs, patients with second-degree Mobitz type II atrioventricular (AV) block, third-degree AV block or sick sinus syndrome that do not wear a pacemaker, and

patients with a baseline QTc interval ≥ 500 milliseconds.

Fingolimod is used to treat multiple sclerosis. Its risk of serious cardiac rhythm disturbances is described in the product information. However, serious adverse events including fatalities have been reported. The contraindications have been introduced to minimize the risk of severe adverse events in patients with cardiac conditions. The warnings and precautions on the immunosuppressive effect of fingolimod potentially leading to serious infections and cancer are also being updated.

- ▶ HPRA. [Third party publication, posted 7 November 2017.](#)

Daclizumab: **Serious liver damage, further restrictions**

European Union – The EMA has recommended further restrictions on the use of the multiple sclerosis medicine daclizumab (Zinbryta®), as an update to the provisional measures introduced in July 2017. A review has found that unpredictable and potentially fatal immune-mediated liver injury can occur during treatment with daclizumab and for up to six months thereafter. Warnings will be added to the product information, and patients and healthcare professionals in the EU will need to sign a form to confirm that they have discussed this risk.

Daclizumab should only be used to treat relapsing forms of multiple sclerosis in patients who have had an inadequate response to at least two disease-modifying therapies (DMTs) and cannot be treated with other DMTs. Daclizumab must not be used in patients with pre-existing liver disease and should not be started in new patients with over two times the upper normal limit

of liver enzymes. It is recommended that daclizumab should not be used in patients with other autoimmune conditions.

Patients' liver function (ALT, AST and bilirubin) should be monitored closely at least once a month before each treatment and for up to six months after treatments have stopped. Patients with liver enzyme levels over three times the upper normal limit should stop taking daclizumab. Patients with signs or symptoms of liver damage and those who test positive for hepatitis B or C infection should be referred to a specialist. If a patient does not comply with monitoring requirements or if the response to treatment is inadequate, treatment discontinuation should be considered.

► [EMA Press release, 10 November 2017.](#)

Levetiracetam: Neuroleptic malignant syndrome

Japan – Following cases of neuroleptic malignant syndrome reported in patients treated with the antiepileptic medicine levetiracetam (Keppra®) in Japan, the PMDA has recommended that the product information should be updated to include information about this risk. Patients treated with levetiracetam should be carefully monitored for signs and symptoms such as fever, muscle rigidity, increased creatinine kinase, tachycardia, blood pressure changes, disturbed consciousness, sweating and increased white blood cells. If neuroleptic malignant syndrome occurs treatment should be discontinued and appropriate measures taken such as cooling of the body, hydration and respiratory management. Decreased renal function with myoglobinuria may also occur in patients treated with levetiracetam.

► [PMDA Summary of investigation results and MHLW Revision of precautions, 17 October 2017.](#)

Sodium polystyrene sulfonate: Separate dosing from other oral medicines

United States of America – The FDA has recommended that the potassium-lowering medicine sodium polystyrene sulfonate (Kayexalate® and related names) should be taken at least 3 hours before or after any other prescription or over-the-counter medicines taken by mouth. That time should be increased to 6 hours for patients with gastroparesis or other conditions resulting in delayed emptying of food from the stomach into the small intestine.

In October 2015 the FDA had requested manufacturers to conduct additional drug interaction studies on sodium polystyrene sulfonate. An *in vitro* study has confirmed that it binds to many commonly prescribed oral medicines, decreasing their absorption and therefore their effectiveness. The product information for medicines containing sodium polystyrene sulfonate is being updated.

► [FDA Drug safety communication, 5 September 2017.](#)

Radium-223 dichloride: Do not use with abiraterone and prednisone or prednisolone

European Union – The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has warned health professionals against the use of the prostate cancer medicine radium-223 dichloride (Xofigo®) in combination with abiraterone (Zytiga®) and prednisone or prednisolone.

This warning follows findings of an increased risk of death and fractures in an ongoing clinical trial. Treatment with Radium-223 dichloride has been stopped

in the trial, and all the patients involved are being monitored closely. The PRAC has started a review of the product.

► [EMA News, 1 December 2017.](#)

Known risks

Amoxicillin: **Thrombocytopenia**

Japan – Following reported cases of thrombocytopenia observed in patients treated with amoxicillin-containing products in Japan, the PMDA has recommended that a warning about this potential adverse effect should be added to the product information. Reversible thrombocytopenia is also listed as a very rare adverse event in the product information for some amoxicillin-containing products approved in the EU.

► [PMDA Summary of investigation results, 17 October 2017.](#)

Moxifloxacin: **Rhabdomyolysis**

Japan – The PMDA has recommended to update the product information for moxifloxacin-containing products to include the risk of rhabdomyolysis. Patients should be monitored, and treatment should be stopped and appropriate measures taken if signs and symptoms of rhabdomyolysis are observed. Health professionals should also be alert to the potential onset of acute kidney injury due to rhabdomyolysis.

The product information for moxifloxacin-containing products approved in the UK states that rhabdomyolysis has been reported very rarely with other fluoroquinolone antibiotics and might possibly also occur during treatment with moxifloxacin.

► [PMDA Summary of investigation results and MHLW Revision of precautions, 17 October 2017.](#)

Palivizumab: **Thrombocytopenia**

Japan – Following reported cases of thrombocytopenia with the immunoglobulin palivizumab (Synagis®) in Japan, the PMDA has recommended that the product information should be updated. Palivizumab is approved in Japan to prevent serious lower respiratory tract infection caused by RSV (respiratory syncytial virus) in neonates and infants. The EU-approved product information includes thrombocytopenia as an uncommon adverse event identified from post-marketing surveillance.

► [PMDA Summary of investigation results and MHLW Revision of precautions, 12 September 2017.](#)

Cladribine: **Progressive multifocal leukoencephalopathy**

Ireland – The marketing authorization holder, in agreement with EMA and HPRA, has informed healthcare professionals that cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported with cladribine (Litak®).

Cladribine is an anti-cancer medicine that can induce myelosuppression and immunosuppression, as well as lymphopenia. It can therefore increase the risk of PML, a rare, potentially fatal demyelinating disease of the brain caused by reactivation of the JC virus. Cladribine is also authorized in Ireland for the treatment of highly active relapsing multiple sclerosis. The product information for this indication already includes a warning about the risk of PML.

► [Direct healthcare professional communication, 1 December 2017.](#)

Clozapine: **Fast-onset intestinal obstruction**

United Kingdom – The MHRA has reminded healthcare professionals of the risk of fast-onset intestinal obstruction, faecal impaction and paralytic ileus associated with clozapine. The adverse effects range from constipation, which is very common, to very rare but serious and potentially fatal events. Particular care should be taken in patients receiving other medicines known to cause constipation, those with a history of colonic disease or lower abdominal surgery, and patients aged 60 years and older. Clozapine is contraindicated in patients with paralytic ileus. Patients should be advised to report constipation immediately. It is vital that constipation is recognized early and actively treated.

The risk of impaired intestinal movement is long established with clozapine; however, health care professionals may not be sufficiently aware of this risk and its potential fast onset.

- ▶ [Drug Safety Update volume 11, issue 3; October 2017: 4.](#)

Buprenorphine, methadone: **Manage risks in opioid-dependent patients taking benzodiazepines**

United States of America – The FDA has advised that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other central nervous system depressants. Although the combined use of these medicines increases the risk of serious side effects (including overdose and death), the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce the risks of serious adverse effects. The

product information for buprenorphine and methadone will be updated accordingly, and detailed recommendations will be included on minimizing the combined use of medication-assisted treatment and benzodiazepines.

- ▶ [FDA Drug Safety Communication, 20 September 2017.](#)

Review outcomes

Factor VIII medicines

European Union – The EMA has concluded that there is no clear and consistent evidence of a difference in the incidence of inhibitor development between factor VIII medicines derived from plasma and those made by recombinant DNA technology.

The risk of inhibitor development will continue to be assessed individually for each product, regardless of class, as more evidence becomes available. The prescribing information of factor VIII medicines will be updated to include, as appropriate, inhibitor development as an adverse effect that is very common in previously untreated patients and uncommon in previously treated patients, and to state that low levels of inhibitors pose less risk of severe bleeding than high levels.

- ▶ [EMA. Factor VIII medicines: no clear and consistent evidence of difference in risk of inhibitor development between classes. 15 September 2017.](#)

Reviews started

Medicine	Use	Concerns	Reviewing authority reference
Hydroxyethyl starch	Management of hypovolaemia	Restrictions were introduced in the EU in 2013 to reduce risks of kidney injury and death. However, the restrictions are not being adhered to.	▶ EMA Press release, 27 October 2017.
Ulipristal (Esmya®)	Treatment of uterine fibroids	Four reports of serious liver injury, three of which ended in liver transplantation. Note: Ulipristal acetate is also the active substance of a single-dose emergency contraceptive, ellaOne®. There are no concerns with ellaOne® at this time.	▶ EMA. Esmya Article-20 procedure – Review started. 1 December 2017.
Febuxostat	Treatment of gout	Preliminary results from a safety clinical trial show an increased risk of heart-related death, and death of all causes, with febuxostat compared to allopurinol.	▶ FDA Drug safety communication, 15 November 2017.
Flupirtine-containing products	Treatment of acute pain in patients who cannot use other analgesics	Continued reports of serious liver problems, despite restrictions introduced in 2013.	▶ EMA Press release, 27 October 2017.
Radium-223 (Xofigo®)	Treatment of metastatic castration-resistant prostate cancer	Increased risk of death and fractures reported in an ongoing clinical trial. While a full investigation is ongoing, doctors in the EU have been advised not to use radium-223 in combination with abiraterone (Zytiga®) and prednisone/prednisolone.	▶ EMA. Xofigo Article-20 procedure – Review started. 1 December 2017.

Non-compliance with good practices

Lupin Ltd.

United States of America – The FDA has sent a warning letter to Lupin Ltd following observations of non-compliance with good manufacturing practice (GMP) at the company's Goa and Indore sites. During FDA inspections of the sites conducted in May 2017 various deficiencies were observed, including inadequate handling of

out-of-specification results in production. The deficiencies were not adequately addressed by the manufacturer's corrective and preventive action. The FDA had found similar shortcomings at the two sites during earlier inspections in 2015 and 2016. The company was requested to immediately and comprehensively assess its global manufacturing operations.

► [FDA Warning Letter 320-18-06, 6 November 2017.](#)

Falsified medicines

Falsified Penicillin V circulating in Cameroon

The WHO Medical Product Alert No. 4/2017 relates to the circulation of **falsified Penicillin V (phenoxymethylpenicillin) circulating in Cameroon.**

Phenoxymethylpenicillin is used to treat particular bacterial infections and is listed as a WHO Essential Medicine and key antibiotic. In September 2017, an NGO identified a product labelled as Pencillin-V Tablets being sold at a street market in the south-west region of Cameroon. Product details are shown below

Product name:	PENICILLIN-V TABLETS
Batch number:	190
Expiry date:	Oct 2019
Manufacturing date:	April 2015
Stated active pharmaceutical ingredient:	Phenoxymetgylpenicillin (with spelling error)
Manufacturer name stated on the label:	OXFORD PHARMA CO. LTD, BELGIUM

Further investigation has revealed the following:

The stated manufacturer does not exist in Belgium. The label contains spelling mistakes and inaccuracies such as the strength/composition.

Laboratory analysis indicates that the tablets do not contain any phenoxymethylpenicillin. Instead each tablet contains 50 mg of paracetamol. The paracetamol content is sufficient to reduce fever if the tablets are taken according to the label directions. This may deceive patients and healthcare professionals into believing that this product is effective, and delay the seeking of an appropriate treatment for the infection. There have been no known adverse reactions reported to WHO at this stage.

► [WHO Medical Product Alert No. 4/2017 \(includes photographs\).](#)

Report suspected falsified products to the competent national regulatory authority and/or pharmacovigilance centre, and notify WHO at rapidalert@who.int.



Regulatory news

Pre-market assessment

China: Regulatory reforms

China – The State Council of China has proposed a number of reforms to the regulatory review and approval system to encourage innovation in medicines and health products. The resources for clinical trials in China will be strengthened, and there will be provisions for acceptance of clinical trial data generated in other countries. Reforms will be introduced to speed up the review and approval for urgently needed health products to meet public health needs. Furthermore, measures are to be introduced to promote drug innovation, with a system linking the review and approval of drugs with their patents, and improving the protection of clinical trial data. (1, 2, 3)

- ▶ (1) State Council of the People's Republic of China. Press release, 9 October 2017.
- (2) Speech Made by Minister Bi Jingquan at the National Videophone Conference on Deepening the Review and Approval System Reform and Encouraging the Drug and Medical Device Innovation (10 October 2017). Posted on 12 October 2017 at: <http://eng.cfda.gov.cn/WS03/CL0757/178430.html>
- (3) *Nature News*, 26 October 2017.

U.S.: Promoting competition for complex products

United States of America – The FDA Commissioner Scott Gottlieb has announced measures to encourage the development and authorization of complex generic medicines, *i.e.* products with one or more features that are difficult to copy such as complex active

ingredients, sites of action, or drug-device combinations. New draft guidance has been issued on pre-approval meeting requests and on the appropriateness of submitting applications for certain peptide products. Workshops will also be held on specific topics to support product development. Additional measures will follow.

These efforts are intended to promote competition for needed complex products to contain the cost of pharmaceuticals.

- ▶ [FDA Voice. Blog post, 2 October 2017.](#)

Europe: Regulators and funders meet

European Union – At a meeting held in September 2017 the EMA and healthcare payer organizations discussed ways to improve access of patients to new medicinal products. The meeting was complementary to the EMA's existing cooperation with health technology assessment (HTA) bodies. The aim is to minimize delays between regulatory approval of a safe and effective medicine, and the pricing and reimbursement negotiations that will determine patients' real access to it.(1)

In November 2011 the EMA and the European Network for Health Technology Assessment (EUnetHTA) published a joint three-year work plan outlining key areas of collaboration. The two organizations will explore their concepts of unmet medical need and therapeutic innovation and of the benefits and added therapeutic value of orphan medicines.(2)

- ▶ (1) [EMA Press release, 27 September 2017.](#)
- (2) [EMA Press release, 13 November 2017.](#)

Australia: Parallel submissions

Australia – Registration submissions for medicines and vaccines that meet certain requirements may now be made under the Therapeutics Goods Administration (TGA) and Pharmaceutical Benefits Advisory Committee (PBAC) arrangements that enable the processes of registration and of reimbursement evaluation and assessment to be undertaken in parallel. Submissions for vaccines must be accompanied by advice from the Australian Technical Advisory Group on Immunisation (ATAGI), and must address any matters raised in that advice.

- ▶ [Pharmaceutical Benefits Scheme \(PBS\). TGA and PBAC Parallel Process and Requirements. Factsheet. 26 September 2017.](#)

EU: Access to clinical data

European Union – One year after its move to publish clinical data submitted in support of marketing authorization applications, the EMA has provided an overview of the response to this flagship policy. As of 20 October 2017 the published data have attracted a total of 3 641 users, of which 697 registered for “non-commercial research purposes”. In an online survey, 62% of respondents found the data useful, and 87% said that the information is presented in an understandable format, despite the redaction or anonymization of certain information in line with European legislation on personal data protection.

- ▶ [EMA Press release, 20 October 2017.](#)

Third tripartite meeting on evaluation of antibiotics

Kyoto – At a tripartite meeting held in Kyoto, Japan, on 24 October 2017 representatives of EMA, FDA and PMDA have taken further steps to align

their approaches to the evaluation of antibiotics. The discussions focused on clinical trial design for certain indications such as uncomplicated gonorrhoea or uncomplicated urinary tract infections, and on streamlining the development of new antibacterial agents for children.

This was the third tripartite meeting on convergence of regulatory requirements for antimicrobial agents. Earlier meetings took place in September 2016 and in April 2017.

- ▶ [EMA News, 17 November 2017.](#)

EU: Ten years of paediatric regulation

European Union – Ten years after the Paediatric Regulation came into force the European Commission has published a report ⁽¹⁾ on progress made with making children’s medicines available. The report concludes that there has been an encouraging increase of new research and new products, but that this is not evenly spread over all therapeutic areas and often linked to research priorities in adults. The report also finds that the paediatric use marketing authorization (PUMA) concept, with its specific reward to incentivize the development of paediatric indications for off-patent products, has failed to deliver.⁽¹⁾

In December 2017 the European Commission announced an evaluation of the legislation on medicines for children, jointly with the legislation on medicines for rare diseases and special populations.⁽²⁾

- ▶ [European Commission. Medicines for Children \[website\].](#)

⁽¹⁾ [Report from the Commission to the European Parliament and the Council. State of Paediatric Medicines in the EU - 10 years of the EU Paediatric Regulation. 26.10.2017.](#)

⁽²⁾ [European Commission. Evaluation of the legislation on medicines for children and rare diseases \(medicines for special populations\).](#)

Post-market monitoring

Operation Pangea X

A total of 123 countries participated in the “Pangea X” international week of action. Operation Pangea is an annual campaign coordinated by Interpol to combat the illegal trade in medicinal products via the internet. This year, regulatory authorities around the world seized more than US\$51 million worth of potentially dangerous medicines and ordered the closure of 3 584 illegal websites. House searches were also conducted and some 400 arrests made. A wide range of products were confiscated, such as erectile dysfunction pills, pain reduction pills, epilepsy medication, anti-psychotic medication and nutritional products, but also antibiotics, which is a cause for concern given the serious and growing threat of antimicrobial resistance. A focus of this year’s Operation Pangea was the fight against illegal trading in fentanyl and its derivatives.

Since its start in 2008 with just eight countries, Operation Pangea has grown exponentially over the past 10 years. This year’s operation saw the highest ever participation of African countries.

► [Interpol News release, 25 September 2017.](#)

Smart Safety Surveillance in LMICs

United Kingdom – The MHRA has announced that it will join the “Project Smart Safety Surveillance” (also known as “Project 3-S”) launched by WHO and the Gates Foundation to help low- and middle-income countries (LMICs) to identify, assess and manage the risks associated with new products. The MHRA’s participation will be for a three-year period, during which three pilots will be run in different LMIC settings.

► [MHRA Press release, 15 December 2017.](#)

See also the article starting on page [575](#).

U.S.: New adverse event dashboard

United States of America – The FDA has launched a new search tool that improves public access to data on adverse events associated with medicines and biologic products submitted to the FDA’s Adverse Event Reporting System (FAERS). The Agency is hoping that the increased transparency will spur the submission of more detailed and complete reports on adverse events from health care professionals and the public.

► [FDA News release, 28 September 2017.](#)
[FDA Adverse Events Reporting System \(FAERS\) Public Dashboard.](#)

Australia: Black triangle scheme

Australia – The TGA has launched its “Black Triangle Scheme” as a simple means to encourage practitioners and patients to report adverse events that may be associated with the use of certain new medicines. A black triangle symbol will appear on product information, patient leaflets and Australian Public Assessment Reports (AusPARs) for the medicines included in the scheme. The scheme will apply to newly registered prescription medicines, except biosimilar medicines and generic versions of previously approved prescription medicines. It also excludes seasonal influenza vaccines, as these are monitored through the AusVaxSafety programme.

A similar Black Triangle Scheme is in operation in the EU.

► [TGA Safety information, 12 October 2017.](#)

EU: Updated pharmacovigilance guidelines

European Union – The EMA has published the following updated pharmacovigilance guideline on its website: Revision 3 of

Module VIII on post-authorization safety studies, Revision 1 of Module IX on signal management and its addendum on methods (finalized post-public consultation), Revision 1 of Module XV on safety communication and related templates (finalized post-public consultation), Revision 4 of Annex I on definitions, and an updated Annex V on abbreviations.

- ▶ EMA. Good pharmacovigilance practices. www.ema.europa.eu – Human regulatory – Post-authorisation – Pharmacovigilance – Good pharmacovigilance practices

EU: Improved EudraVigilance system launched

European Union – The EMA has launched a new and improved version of EudraVigilance, the European information system of suspected adverse reactions to medicines in the European Economic Area (EEA). The system offers improved features for reporting and public access to data. The reports of individual cases of suspected adverse reactions will be made available to the WHO Uppsala Monitoring Centre (UMC) directly from EudraVigilance.

With the launch, further legal obligations for marketing authorization holders became applicable to the mandatory reporting through EudraVigilance. Spontaneous reporting by patients and healthcare professionals through local reporting systems, as well as reporting of adverse reactions during clinical trials, remain unchanged.

- ▶ EMA News, 22 November 2017.
Public access to EudraVigilance data: www.adrreports.eu

Variations

Australia: Automated notifications

Australia – An online notification process for very low risk changes to all registered medicines is being introduced in Australia. Manufacturers can submit an online form requesting such changes, along with legal assurances that the conditions for the specific variation are met. Upon payment of fees the requests will be automatically processed and the changes to the medicine can be implemented.

The process started in July 2017 with non-prescription medicines, and was extended to prescription medicines in December 2017. Additional types of variations that could be processed through this route have been proposed for both prescription and non-prescription medicines; however they will first need to be included in the relevant Regulations.

- ▶ TGA notice, 2 November 2017.
TGA. [Notifications process: Requests to vary biologicals and registered medicines where quality, safety and efficacy are not affected](#). Version 2.0, December 2017. Posted 23 November 2017.

Labelling

U.S.: Antimicrobials

United States of America – A new, dedicated FDA web page will list updated, FDA-recognized “breakpoints” for antimicrobial active ingredients, showing whether specific bacteria or fungi are susceptible to antibacterial or antifungal medicines. Under the new approach manufacturers will reference the FDA web page in their product information, instead of updating it continuously with new breakpoint information from susceptibility testing.

- ▶ FDA News release, 13 December 2017.

EU: Excipients

European Union – The European Commission has adopted a revised annex to the guidelines on declaring excipients in the labelling and package leaflet of medicinal products for human use. Five new excipients need to be declared, and new safety warnings are to be included for ten excipients that were previously listed in the annex.

The revised requirements apply to both centrally and nationally authorized products. For new marketing authorization applications they will be effective from the day of its publication. For authorized medicines, marketing authorization holders should submit revised wording in line with the new requirements at the earliest opportunity, or submit a variation within three years after the publication of the revised annex.

► [EMA News, 9 October 2017.](#)

Canada: Prescription opioids

Canada – Health Canada has convened a scientific advisory panel on opioid use and contraindications, and is working with manufacturers to update the product information of all prescription opioid products in line with the panel's recommendations. The revised product information will recommend a limited quantity and duration of opioid prescriptions for acute pain, and a daily threshold dose of 50–90 morphine milligram equivalents per day for chronic pain except in cancer patients and palliative care and will include clearer warnings on the risks of opioids generally and in special patient groups.

► [Health Canada Information update, 8 December 2017.](#)

Product-specific frameworks

Canada: Antimicrobials

Canada – The Government of Canada has released its *Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action*. The Framework was developed jointly with provinces and territories and other key partners in the human and animal health sectors to guide collective action in four areas: surveillance, stewardship, infection prevention and control, and research and innovation. A Pan-Canadian Action Plan will be developed to put the Framework into use.⁽¹⁾

In November 2017 two new rules to fight the growing problem of antimicrobial resistance came into force. Firstly, livestock owners may no longer import antimicrobials that are important to human health, but only medicines that do not pose a risk to human health or food safety, and only in limited quantities. Secondly, a new programme will facilitate importation and sale of low risk veterinary health products such as vitamin and mineral supplements.⁽²⁾

► ⁽¹⁾ [Health Canada News release, 5 September 2017.](#)

⁽²⁾ [Health Canada News release, 14 November 2017.](#)

EU: Advanced therapies

European Union – The European Commission (EC)'s Directorate-General for Health and Food Safety (DG SANTE) and the European Medicines Agency (EMA) have published an action plan aiming to streamline regulatory procedures for advanced therapy medicinal products (ATMPs) and address the specific requirements of developers better. The plan contains 19 actions in different key areas. These include the proposed development

of an EC guideline on good manufacturing practices for advanced therapies, dialogue with national regulatory authorities about the interplay between the legislation on genetically modified organisms and that on medicines, and clarification of expectations for investigational ATMPs.(1)

ATMPs are medicines for human use that are based on genes or cells. They offer ground-breaking opportunities for the treatment of diseases and injuries. They are particularly important for severe, untreatable or chronic diseases for which conventional approaches have proven to be inadequate.

In November 2017 the European Commission published a set of guidelines on good manufacturing practice (GMP) for ATMPs. The new guidelines address the novel and complex manufacturing scenarios for these products and foster a risk-based approach to manufacture and testing.(2)

► (1) [EMA News, 20 October 2017.](#)

(2) [EMA News, 24 November 2017.](#)

U.S.: Regenerative medicine products

United States of America – The FDA has announced a comprehensive policy framework for the development and oversight of regenerative medicine products, including novel cellular therapies. The framework is outlined in a suite of four guidance documents, of which two are final and two are drafts for public comment. The new guidance describes what products are regulated as medicines, devices, and/or biological products and proposes a science-based process for evaluating the safety and effectiveness of regenerative therapies while supporting development in this area. It also sets out a risk-based framework for

enforcement actions against products that raise potential significant safety concerns.

► [FDA News release, 16 November 2017.](#)

Australia: Autologous products

Australia – The TGA will introduce changes to the regulation of autologous human cell and tissue products, including so-called “autologous stem cell” therapies. The level of oversight will be determined by the risk posed to patient safety. Certain products will be in the remit of the TGA, while others will fall under the Biologicals Regulatory Framework. Detailed guidance on the new approach is being drafted. The changes are expected to commence in early 2018, with a transition period for implementation.

Autologous human cell and tissue products have previously been outside TGA's regulatory oversight because historically they have been seen as an extension of medical practice. The new approach will bring Australia into closer alignment with other regulators.

► [TGA Media release, 24 October 2017.](#)

Medical devices

India: Classification list

India – The Drug Controller General of India has published a list of medical devices and in vitro diagnostics together with their risk classifications that will apply under the Medical Devices Rules, 2017. Four classes for medical devices are defined, with more stringent regulatory controls in place for products classified as having a higher risk in terms of public health.

The Rules will enter into force on 1 January 2018. The list will be updated from time to time.

► [CDSCO Notice, 1 November 2017.](#)

UK: Guide to new EU requirements

United Kingdom – The MHRA has launched an interactive guide to introduce manufacturers to their obligations under the new EU regulations for medical devices and in vitro diagnostic devices.

The new regulations are being phased in since 25 May 2017 and will apply across EU Member States from 26 May 2020 and 2022 respectively. They introduce stronger requirements for traceability of products throughout the supply chain with a unique device identification (UDI) system, new standards for clinical evidence, more rigorous vigilance reporting requirements and clearer requirements on post-market surveillance.

► [MHRA Press release, 29 August 2017.](#)

Collaboration

EU-FDA mutual recognition agreement on inspections

The EU-FDA mutual recognition agreement on good manufacturing practice (GMP) inspections came into force on 1 November 2017. This is an unprecedented step, as the FDA has never before recognized another country's inspectorate. The mutual recognition agreement will enable more efficient global pharmaceutical manufacturing inspections.

In June 2017, the European Commission had determined that the FDA's GMP inspections are at a level equivalent to the EU, and in October 2017 the FDA completed its capability assessments of 8 European national regulatory authorities; the others will be assessed by July 2019. The agreement initially covers inspections of sites manufacturing medicinal products for human use.

Veterinary products will be added by July 2019, and vaccines and plasma-derived medicinal products by July 2022.

► [FDA News release, 31 October 2017.](#)

[European Commission. E-news, 31 October 2017.](#)

[EMA Press release, 31 October 2017.](#)

Singapore joins ICH

Geneva – At the ICH meeting held in Geneva in November 2017 the Health Sciences Authority (HSA) of Singapore has been accepted as a new regulatory member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The ICH Assembly also approved the Instituto Nacional de Vigilancia de Medicamentos y Alimentos of Colombia (INVIMA) and the Bill & Melinda Gates Foundation as new observers.

► [ICH Press release, 30 November 2017.](#)

[HSA Press release, 30 November 2017.](#)

IGDRP and IPRF merge

The International Generic Drug Regulators Programme (IGDRP) and the International Pharmaceutical Regulators Forum (IPRF) have agreed to consolidate their operations. Together they will form a the International Pharmaceutical Regulators Programme (IPRP), to be officially launched on 1 January 2018. IPRP aims to provide a regulatory hub for information exchange and cooperation on all medicinal products in order to maximize synergies and simplify the numerous forms of international regulatory collaboration.

► [IPRF News, 8 December 2017.](#)

[IGDRP News, 8 December 2017](#)

Regulatory summit and ICMRA meeting

Japan – From 23–26 October 2017 the international Summit of Heads of Medicines Regulatory Agencies and the meeting of the International Coalition of Medicines Regulatory Authorities (ICMRA) were held in Kyoto, Japan.⁽¹⁾ At the meeting, the ICMRA launched its Strategic Priority on Innovation (SPI), identifying the issues that the Coalition aims to address. An overview is provided in a formal concept note.⁽²⁾

- ▶ ⁽¹⁾ PMDA Notice, 27 October 2017.
- ▶ ⁽²⁾ ICMRA. Strategic Priority on Innovation – Concept Note. 11 December 2017.

Generic work-sharing trial

The regulatory authorities of Australia, Canada, Singapore and Switzerland (ACSS) have invited marketing authorization applications for assessment under their newly launched Generic Medicines Work Sharing Trial. Applications should be submitted simultaneously to at least two, but preferably more, of the ACSS Consortium members.

- ▶ TGA. ACSS - Generic Medicine Work Sharing Trial. 6 December 2017.

Under discussion

European Union – The EMA has opened two public consultations related to **herbal medicines**: *A Draft procedure for the review and revision of European Union herbal monographs and European Union list entries* ⁽¹⁾ and a *Concept paper on the development of a reflection paper on new analytical methods/ technologies in the quality control of herbal medicinal products* ⁽²⁾.

- ▶ ⁽¹⁾ EMA Consultation, 27 October 2017.
 - ▶ ⁽²⁾ EMA Consultation, 31 October 2017.
- Closing date: 30 April 2018.

European Union – The EMA has released a new guideline to support and facilitate the development of vaccines and medicines

to prevent and treat infections caused by **respiratory syncytial virus (RSV)**.

- ▶ EMA News, 30 October 2017.
- Closing date: 30 April 2018.

European Union – The EMA is seeking feedback from all stakeholders (patients and consumers, healthcare professionals, pharmaceutical industry and national competent authorities) on their use of **electronically or digitally delivered medicinal product information**. A mapping of ongoing initiatives will be used in a workshop to be held in 2018 to develop key principles for the use of electronic formats.

- ▶ EMA News, 15 November 2017.
- Closing date: 28 February 2018.

Under discussion

United States of America – The FDA has published two draft guidance documents for industry related to its new framework on **regenerative medicine products**.

- ▶ Federal Register Notice, 17 November 2017. [Evaluation of Devices Used With Regenerative Medicine Advanced Therapies](#).
Federal Register Notice, 17 November 2017. [Expedited Programs for Regenerative Medicine Therapies for Serious Conditions](#).
Closing date: 15 February 2018.

United States of America – The FDA has held a public hearing about potential pathways for approval of a device intended to be used with a medicine that is already on the market, when the marketing authorization holder of the medicine does not wish to pursue the new use. Such so-called **devices referencing drugs** could advance public health by offering new uses with approved drugs. Independently of the public hearing, comments can be submitted to the public docket.

- ▶ FDA. [Devices Referencing Drugs; Public Hearing; Request for Comments \[webpage\]](#).
Closing date: 15 January 2018.

European Union – The EMA has launched a public consultation on **supplementary protection certificates (SPCs) and patent research exemptions**. SPCs are a unique intellectual property right that constitute an extension of up to 5 years to the term of a patent right of 20 years to offset the time spent on pre-approval testing and clinical trials. Aspects under consideration include the creation of a European SPC title, an update of the scope of EU patent research exemptions, and the introduction of an SPC manufacturing waiver.

- ▶ [EMA Consultation, 12 October 2017](#).
Closing date: 4 January 2018.

United States of America – The FDA has released draft guidance delineating its new **Breakthrough Devices Program**. Building on the Expedited Access Pathway (EAP) programme, this new pathway is intended to speed up patients' access to medical devices that more effectively diagnose or treat life-threatening or irreversibly debilitating diseases or conditions, including technologies that have no alternative or that offer a significant advantage over FDA-cleared or approved alternatives.

- ▶ [Federal Register Notice, 25 October 2017](#).
Closing date: 26 December 2017.
See also: [FDA Statement, 24 October 2017](#).

European Union – The European Commission (EC) has published a proposed amendment to its Regulation No 847/2000 on orphan drug products with regard to the definition of the concept of **similar medicinal products**. The update is proposed in the light of major developments in the field of biological medicines, especially with regard to advanced therapy medicinal products.

- ▶ [EC Draft regulation, 30 October 2017](#).
Closing date: 27 November 2017.

Australia – The TGA has proposed a set of reforms for **evaluation of complementary medicines**. Among other things it is proposed to introduce a third assessment pathway that would be sitting between the existing listed medicine (low risk) and registered medicine (higher risk) pathways, and to use reports from comparable overseas regulators in assessing ingredients and products under the new pathway.

- ▶ [TGA Consultation, 26 September 2017](#).
Closing date: 7 November 2017.

Approved

Semaglutide

Product name: Ozempic®

Dosage form: Injection for subcutaneous use

Class: Glucagon-like peptide 1 (GLP-1) receptor agonist

Approval: FDA

Use: Adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus

Benefits: Ability to reduce HbA1c levels.

Safety information: In rodents, semaglutide causes thyroid C-cell tumors. Semaglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2).

► [FDA prescribing information, revised 12/2017.](#)

Vestronidase alfa for rare enzyme disorder

Non-proprietary name in the U.S.: Vestronidase alfa-vjvk¹

Product name: Mepsevii®

Dosage form: Injection for intravenous use

Class: Recombinant human lysosomal beta glucuronidase, enzyme replacement therapy;
ATC code: A16AB18

Approval: FDA (fast track designation, priority review; orphan drug designation)

Use: Treatment of mucopolysaccharidosis type VII (MPS VII), also known as Sly syndrome, an extremely rare, progressive genetic condition that affects most tissues and organs.

Benefits: First approved treatment for MPS VII.

¹ This FDA-approved biological is one of the first to receive a four-letter suffix to its nonproprietary name in the U.S. Previously, such suffixes were only added to the names of biosimilars.

Source: Regulatory Affairs Professional Society (RAPS). [FDA Begins Adding Suffixes to Newly Approved Biologics' Names](#). Posted by Zachary Brennan on 17 November 2017.

Safety information: Anaphylaxis has occurred with administration of vestronidase alfa-vjvk as early as the first dose. Appropriate support should be readily available, and patients should be observed closely during and for 60 minutes after infusion. In case of anaphylaxis, infusion should be stopped immediately.^(1,2)

► ⁽¹⁾ [FDA News release, 15 November 2017.](#)

⁽²⁾ [Prescribing information for Mepsevii; revised 11/2017.](#)

Rurioctocog alfa pegol for haemophilia A

Product name: Adynovi®

Dosage form: Powder and solvent for solution for injection

Class: Recombinant human factor VIII;
ATC code: B02BD02

Approval: EMA

Use: Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency)

Benefits: Ability to prevent and control bleeding when used on demand and during surgical procedures.

► [EMA/CHMP Summary of opinion, 9 November 2017.](#)

Emicizumab for haemophilia A

Nonproprietary name in the U.S.: Emicizumab-kxwh²

Product name: Hemlibra®

Dosage form: Subcutaneous injection

Class: Systemic haemostatic; *ATC code:* B02BX06

Approval: FDA (priority review, breakthrough therapy designation; orphan drug designation)

Use: To prevent or reduce the frequency of bleeding episodes in adults and children with haemophilia A who have developed Factor VIII inhibitors.

² See Footnote 1

Approved

Benefits: Fewer bleeding episodes and patient-reported improvement in haemophilia-related symptoms and physical functioning.

Safety information: Severe blood clots (thrombotic microangiopathy and thromboembolism) have been observed in patients who were also given activated prothrombin complex concentrate as rescue treatment for bleeds for 24 hours or more while taking emicizumab-kxwh.

► (1) [FDA Press release, 16 November 2017.](#)

Non-live recombinant zoster vaccine (adjuvanted)

Product name: Shingrix®

Dosage form: Suspension for intramuscular injection

Class: Viral vaccine

Approval: Health Canada

Use: Prevention of *H. zoster* infection in adults.

Benefits: In a pooled analysis of clinical studies, the vaccine demonstrated efficacy against *H. zoster* of greater than 90% in adults aged 50 and older and in those aged 70 and older. Efficacy was sustained during the four-year follow-up period.

Notes: Canada is the first country to approve this vaccine. It is also under review in the U.S., the EU, Australia and Japan.

► [Health Canada. Regulatory decision summary for Shingrix. 13 October 2017.](#)

Padeliporfin for prostate cancer

Product name: Tookad®

Dosage form: Powder for solution for injection

Class: Sensitizer used in photodynamic/radiation therapy; *ATC code:* L01XD07

Approval: EMA

Use: Treatment of adults with previously untreated, unilateral, low-risk adenocarcinoma of the prostate.

Benefits: Higher probability of negative biopsy at 24 months, and delayed disease progression, compared with active surveillance.

Safety information: For hospital use only.

► [EMA/CHMP Opinion, 14 September 2017.](#)

Dolutegravir and rilpivirine for HIV infection

Product name: Juluca®

Dosage form: Fixed-dose combination tablet

Class: Antiviral combination for treatment of HIV infection; *ATC code:* J05AR21

Approval: FDA

Use: Treatment of adults with HIV-1 infections whose virus has been suppressed on a stable regimen for at least six months, with no history of treatment failure and no known substitutions associated with resistance to dolutegravir or rilpivirine.

Benefits: As effective as other HIV regimens and potentially less toxic due to the reduced number of active ingredients.

Notes: This is the first FDA-approved complete treatment regimen containing only two antiretrovirals.

► [FDA News release, 21 November 2017.](#)

Letermovir to prevent CMV after stem cell transplant

Product name: Prevydis®

Dosage form: Concentrate for solution for infusion; film-coated tablets

Class: Antiviral medicine; *ATC code:* J05AX18

Approval: EMA (orphan designation)

Use: Prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant.

Benefits: Better tolerated than other antiviral agents approved for the same indication.

► [EMA Press release, 10 November 2017.](#)

Copanlisib for relapsed follicular lymphoma

Product name: Aliqopa®

Dosage form: Injection

Approved

Class: Kinase inhibitor**Approval:** FDA (accelerated approval, priority review; orphan drug designation)**Use:** treatment of adults with relapsed follicular lymphoma who have received at least two prior systemic therapies.**Benefits:** Complete or partial shrinkage of tumours in clinical trials.**Safety information:** Serious side effects include infections, hyperglycaemia, hypertension, non-infectious pneumonitis, neutropenia and severe skin reactions. Copanlisib should not be used in pregnant or breastfeeding women.► [FDA News release, 14 September 2017.](#)**Abemaciclib for certain breast cancers****Product name:** Verzenio®**Dosage form:** Oral tablet**Class:** Inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6)**Approval:** FDA (priority review, breakthrough therapy)**Use:** Treatment of adults with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer that has progressed after endocrine therapy.**Benefits:** Longer median progression-free survival in clinical trials.**Safety information:** Serious side effects include diarrhoea, neutropenia, elevated liver blood tests and deep venous thrombosis/pulmonary embolism. Abemaciclib may cause harm to a developing foetus.► [FDA News release, 28 September 2017.](#)**Acalabrutinib for mantle cell lymphoma****Product name:** Calquence®**Dosage form:** Capsules for oral use**Class:** Kinase inhibitor**Approval:** FDA (accelerated approval, priority review, breakthrough therapy, orphan drug designation)**Use:** Treatment of adults with mantle cell lymphoma who have received at least one prior therapy.**Benefits:** Complete or partial response observed in 81% of patients in initial study.**Safety information:** Serious side effects include bleeding, infections and atrial fibrillation. Additional cancers have occurred in some patients taking acalabrutinib. Women who are breastfeeding should not take acalabrutinib because it may cause harm to a newborn baby.► [FDA News release, 31 October 2017.](#)**Benralizumab for eosinophilic asthma****Product name:** Fasenra®**Dosage form:** Solution for injection in pre-filled syringes**Class:** Anti-eosinophil, humanized monoclonal antibody; *ATC code:* R03DX10**Approval:** EMA**Use:** Add-on maintenance treatment in adult patients with severe eosinophilic asthma that is inadequately controlled despite high-dose inhaled corticosteroids plus long-acting beta-agonists.**Benefits:** Significant reductions in annual exacerbation rates of eosinophilic asthma, especially in patients with more than 300 eosinophils per microlitre of blood before treatment.► [EMA/CHMP Summary of opinion, 9 November 2017.](#)**Latanoprostene bunod for glaucoma****Product name:** Vyzulta®**Dosage form:** Ophthalmic solution 0.024%, for topical ophthalmic use**Class:** Prostaglandine analog**Approval:** FDA**Use:** Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Approved

Benefits: Sustained lowering effect on intraocular pressure.

- ▶ Prescribing information for Vyzulta®, Revised 11/2017

Gene cell therapy

Axicabtagene ciloleucel for certain B-cell lymphomas

Product name: Yescarta®

Dosage form: Cell suspension for infusion, for autologous use

Class: Autologous chimeric antigen receptor (CAR) T cell therapy

Approval: FDA (priority review, breakthrough therapy; orphan drug designation)

Use: Treatment of adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment. The product is not indicated for the treatment of patients with primary central nervous system lymphoma.

Benefits: Ability to induce complete remission lasting several months.

Safety information: Severe side effects include cytokine release syndrome (CRS) and neurologic toxicities, both of which can be fatal or life-threatening. Other side effects include serious infections, low blood cell counts and a weakened immune system.

- ▶ FDA News release, 18 October 2017.

Biosimilars

Insulin lispro

Product name: Admelog®

Reference product: Humalog®

Approval: FDA (abbreviated approval as a “follow-on product” through the 505(b)(2) pathway)

Use: To improve control in blood sugar levels in adults and children aged 3 years and older

with type 1 diabetes mellitus, and adults with type 2 diabetes mellitus.

- ▶ FDA News release, 11 December 2017.

Trastuzumab

(1)

Product name: Ontruzant®

Reference product: Herceptin®

Approval: EMA

Use: Treatment of early and metastatic breast cancer, and metastatic gastric cancer.

- ▶ EMA/CHMP Summary of opinion, 14 September 2017.

(2)

Nonproprietary name in the U.S.: Trastuzumab-dkst

Product name: Ogivri®

Reference product: Humira®

Approval: FDA

Use: Treatment of patients with breast or metastatic stomach cancer (gastric or gastroesophageal junction adenocarcinoma) whose tumours overexpress the HER2 gene (HER2+)

- ▶ FDA News release, 1 December 2017.

Bevacizumab

Product name: Mvasi®

Reference product: Avastin®

Approval: EMA

Use: Treatment of certain advanced, metastatic or recurrent cancers.

- ▶ EMA/CHMP Summary of opinion, 9 November 2017.

Filgrastim (South Africa)

Product: Filgrastim from Teva Pharmaceutical Industries (Teva)

Reference product: Neupogen®

Approval: Medicines Control Council (MCC), South Africa

Approved

Use: 1. peripheral blood stem cell harvesting in autologous stem cell harvesting in haematological malignancies; 2. chemotherapy-induced febrile neutropenia

Note: This is the first non-originator biological medicine approved in South Africa.

► [GaBI News, 1 December 2017.](#)

Adelimumab

Product name: Cyltezo®

Reference product: Humira®

Approval: EMA

Use: Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis.

► [EMA/CHMP Summary of opinion, 14 September 2017.](#)

Novel dosage forms

Orodispersible budesonide for a rare condition of the oesophagus

Product name: Jorveza®

Dosage form: Orodispersible tablets

Class: Locally acting corticosteroid;
ATC code: A07EA06

Approval: EMA (accelerated approval, orphan designation)

Use: Treatment of eosinophilic oesophagitis in patients over 18 years of age.

Benefits: Ability to reduce eosinophil infiltrations into the oesophageal mucosa and reduce symptoms such as dysphagia and pain during swallowing.

Note: Budesonide as inhalation spray has been used off-label to treat patients with eosinophilic oesophagitis and the effects of this use have been extensively described in scientific literature.

► [EMA Press release, 10 November 2017.](#)

Aripiprazole with tracking sensor

Product name: Abilify MyCite®

Dosage form: Tablet with embedded ingestible sensor

Class: Antipsychotic; *ATC code:* N05AX12

Approval: FDA

Use: Treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder, and add-on treatment for depression in adults.

Benefits: Ability to track the ingestion of a medication prescribed for a mental illness.

Safety information: Aripiprazole is not approved to treat patients with dementia-related psychosis. Its safety and effectiveness in children have not been proven. Patients should be monitored for worsening and emergence of suicidal thoughts and behaviours.

It has not been shown whether the product can improve patients' compliance with their treatment regimen. The system should not be used to track drug ingestion in real time or during an emergency because detection may be delayed or may not occur.

► [FDA News release, 13 November 2017.](#)

Once-monthly buprenorphine for opioid use disorder

Product name: Sublocade®

Dosage form: Drug-device combination utilizing buprenorphine and the Atrigel Delivery System in a pre-filled syringe.

Class: Medicine used in opioid dependence;
ATC code: N07BC

Approval: FDA (fast track designation, priority review)

Use: Treatment of moderate-to-severe opioid use disorder in adult patients who have initiated treatment with a transmucosal buprenorphine-containing product and have been on a stable dose of buprenorphine treatment for at least seven days.

Benefits: Reduced medication burden, potentially promoting adherence.

Approved

Safety information: The product carries a boxed warning about the risks of intravenous self-administration, which could cause occlusion, tissue damage or embolus and could be fatal. The product is to be administered only by health care professionals and will be provided to them through a restricted programme.

► [FDA News release, 30 November 2017.](#)

Extensions of indications

Sunitinib to reduce the risk of relapsing kidney cancer

Product name: Sutent®

Approval: FDA

Newly approved use: Adjuvant treatment for adult patients at a high risk of kidney cancer returning after nephrectomy. First FDA-approved product for this use.

Safety information: Risk of severe liver damage, which may result in liver failure or death.

► [FDA News release, 16 November 2017.](#)

Vemurafenib for rare blood cancer

Product name: Zelboraf®

Approval: FDA (priority review, breakthrough therapy; orphan drug designation)

Newly approved use: Treatment of adult patients with BRAF V600 mutation-positive Erdheim-Chester Disease, a rare type of blood cancer.

► [FDA News release, 6 November 2017.](#)

Mepolizumab to treat a rare autoimmune disease

Product name: Nucala®

Approval: FDA (priority review; orphan drug designation)

Newly approved use: Treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA), a rare autoimmune disease that causes vasculitis, an inflammation in the wall of blood vessels of the body.

► [FDA News release, 12 December 2017.](#)

Diagnostics

Next-generation sequencing (NGS) cancer profiling tests

(1)

Product name: IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets) tumour profiling test (assay)

Approval: FDA

Use: This in vitro diagnostic test can identify genetic cancer mutations in 468 unique genes.

Notes: The FDA has announced the recent accreditation of the New York State Department of Health (NYSDOH) as an third-party reviewer of in vitro diagnostics submitted for FDA review.

Along with this authorization, the FDA has established a Class II regulatory pathway for the review of other NGS-based tumour profiling tests for use in patients diagnosed with cancer.

► [FDA News release, 15 November 2017.](#)

(2)

Product name: FoundationOne CDx (F1CDx)®

Approval: FDA (breakthrough device designation)

Use: Detection of genetic mutations in 324 genes and two genomic signatures in any solid tumour type.

Note: The Centers for Medicare & Medicaid Services (CMS) at the same time proposed coverage of the F1CDx, after overlapping review by the FDA and CMS under the Parallel Review Program, which facilitates earlier access to innovative medical technologies for Medicare beneficiaries.

► [FDA News release, 30 November 2017.](#) ◊

Publications and events

Access to medicines

Hepatitis C medicines landscape

Geneva – Unitaid has published a landscape analysis of the current state of technologies for the treatment of hepatitis C virus (HCV) and of the market dynamics that affect access to HCV medicines.

The report finds that DAAs are now becoming more widely available and affordable, but intellectual property barriers have created a dual market with prices remaining high in some countries. However, even where generics are available at affordable prices financing is lacking, and there is too little screening and demand for HCV testing. The market for generics has developed fast but remains fragile because of the uncertain demand and uptake.⁽¹⁾

In October 2017 the international humanitarian organization Médecins Sans Frontières (MSF) announced that it has secured deals for the two key DAAs sofosbuvir and daclatasvir at US\$120 per 12-week treatment course. MSF's work on HCV is partially supported by UNITAID.⁽²⁾

► ⁽¹⁾ Unitaid, WHO. [Technology and Market Landscape. Hepatitis C medicines. August 2017.](#)

⁽²⁾ MSF Press release, 31 October 2017.

MPP licence for bicittegravir

Geneva – The Medicines Patent Pool (MPP) and Gilead Sciences have signed a licence for bicittegravir, an integrase inhibitor which is under review in the U.S. and the EU as part of a once-daily, single-tablet HIV regimen. The licence allows manufacturers to develop

and sell generic medicines containing bicittegravir, if approved in the U.S., in 116 low- and middle-income countries where more than 30 million people live with HIV.

The MPP and Gilead are also expanding the geographical scope of licences on other HIV products, enabling generic medicines to be supplied to additional countries.⁽¹⁾

In December 2017, the MPP announced that it will include information on anti-cancer products in its patent and licensing database, MedsPaL, as a first step in upgrading the database to include all patented treatments on WHO essential medicines list.⁽²⁾

► ⁽¹⁾ MPP Press release, 4 October 2017.

⁽²⁾ MPP Highlight, 12 December 2017.

New methodologies for Access to Medicine Index

Amsterdam – The Access to Medicine Foundation has published the updated methodology for its 2018 Access to Medicine Index. This latest methodology focuses on areas where the 20 major pharmaceutical companies assessed in the Index have the greatest potential to make a difference. New indicators have been developed in response to changing global health priorities, including one that captures how companies are responding to R&D priorities set by WHO and others, and new metrics that will evaluate the quality of access initiatives and how impact is being assessed. The 2018 Index will also assess companies' actions in relation to cancer for the first time, along with their actions on 76 other high-burden diseases, conditions and pathogens.⁽¹⁾

In August 2017 the Foundation had published the methodology for its 2018 Antimicrobial Resistance Benchmark, the first independent framework for assessing action by pharmaceutical companies to combat antimicrobial resistance.⁽²⁾ The first antimicrobial benchmark report is expected to be published in early 2018.

► (1) [Access to Medicine Foundation. News, 5 October 2017.](#)

(2) [Access to Medicine Foundation. News, 24 August 2017.](#)

Safety and efficacy of medicines

Expedited approval and label changes

A study of 382 FDA-approved medicines found that products approved through expedited pathways had more safety-related label changes after approval, particularly for the types of changes representing the highest risk warnings. The authors recommend that the reasons for this finding should be explored to inform appropriate policy interventions.

Of 382 new pharmaceutical products included in the study, 135 (35%) were associated with an expedited development or review pathway. Products approved through an expedited pathway had a 48% higher rate of changes to boxed warnings and contraindications than those approved through other pathways, and of 67 changes to boxed warning sections reviewed in the study only 3 served to describe reduced risks for patients.

► Mostaghim S, Gagne JJ, Kesselheim AS. Safety related label changes for new drugs after approval in the US through expedited regulatory pathways: retrospective cohort study. *BMJ* 2017;358:j3837. doi: <https://doi.org/10.1136/bmj.j3837>

Real-world data may support new indications

A newly published study used insurance claims data from a nationwide health care database to compare outcomes of patients newly prescribed telmisartan or ramipril. The study replicated the inclusion and exclusion criteria of a randomized clinical trial (the ONTARGET trial) that established a supplemental indication for telmisartan, and used propensity score matching to balance 74 patient characteristics. Similar to the randomized clinical trial, the study based on real-world data revealed a decreased risk of angioedema with telmisartan compared with ramipril. The authors conclude that in certain situations database studies may support the demonstration of effectiveness of approved medications in applications for additional indications.

► Fralick M, Kesselheim AS, Avorn J, Schneeweiss S. Use of Health Care Databases to Support Supplemental Indications of Approved Medications. *JAMA Intern Med.* Published online November 20, 2017. doi:10.1001/jamainternmed.2017.3919.

Medicines quality

One in ten medical product in developing countries is substandard or falsified

Geneva – Two new WHO reports suggest that an estimated one in ten medical products in developing countries is substandard and falsified, meaning that hundreds of thousands of people die or suffer grave health consequences from such products every year. The first report is based on data collected by the Global Surveillance and Monitoring System for substandard and falsified medicines, vaccines and in-vitro diagnostic tests during its first four years of operation.⁽¹⁾ The second is a study on the

public health and socioeconomic impact of substandard or falsified medical products in low- and middle-income countries.⁽²⁾

Although more research is needed to estimate the threat posed by substandard and falsified medical products more accurately, these results are a stark reminder that all countries must work together to prevent the traffic of these products and improve detection and response.

► [WHO News, 28 November 2017.](#)

⁽¹⁾ [WHO Global Surveillance and Monitoring System for substandard and falsified medical products.](#) ISBN: 978-92-4-151342-5. November 2017.

⁽²⁾ [WHO. A study on the public health and socioeconomic impact of substandard and falsified medical products.](#) ISBN: 978-92-4-151343-2.

Quality of cardiac drugs in Africa

A sample testing study of seven routinely used cardiovascular medications (anticoagulants, antihypertensives and statins) in ten Sub-Saharan African countries found a significant proportion of poor quality products at licensed pharmacies and unlicensed street-markets. Of 1 530 samples tested, 16.3% had a content of active ingredient below 85% or above 105% of that declared on the packaging. The proportion of substandard products was particularly high for amlodipine (29%), captopril (26%), generic products (23%), and for medicines produced in Asia (35%). 50% of drugs produced in Asia and sold in street-markets were found to be substandard. The authors conclude that continued monitoring strategies are required to fight poor quality medicines.

► [Antignac M, Diop BI, Macquart de Terline D et al. Fighting fake medicines: First quality evaluation of cardiac drugs in Africa.](#) *Int J Cardiol.* 2017;243:523-28.

Survey of antimalarials in Myanmar

A survey of 153 artemisinin-containing antimalarial samples purchased in private drug stores in different regions of Myanmar found that more than 35% of the collected drugs were oral artesunate and artemether monotherapies, which are not recommended for the treatment of malaria. The survey also provided the first description of falsified parenteral artesunate circulating on the market. The authors call for more oversight of medicines quality by regulatory authorities.

► [Guo S, Kyaw MP, He L, Min M, Ning X, Zhang W, Wang B, Cui L. Quality Testing of Artemisinin-Based Antimalarial Drugs in Myanmar.](#) *Am J Trop Med Hyg.* 2017 Oct;97(4):1198-1203. doi: 10.4269/ajtmh.17-0305.

Public health updates

Antibiotic resistance

The pipeline is running dry

Geneva – A new WHO analysis confirms that the world is running out of new antibiotics to combat the growing threat of antimicrobial resistance. A review of new antibiotics and biologicals in clinical development shows that very few of them will add value to the current treatment arsenal for the 13 WHO-identified priority pathogens, and that there are very few oral antibiotics in the pipeline although these are essential for treating infections outside hospitals or in resource-limited settings.

To counter this threat, WHO and the Drugs for Neglected Diseases Initiative (DNDi) have set up the Global Antibiotic Research and Development Partnership (GARDP). Germany, Luxembourg, the Netherlands, South Africa, Switzerland, the United Kingdom and the

Public health updates

Wellcome Trust have pledged more than €56 million for the development of new treatments.

- ▶ [WHO News release, 20 September 2017.](#)
WHO. [Antibacterial agents in clinical development. An analysis of the antibacterial clinical development pipeline, including tuberculosis.](#) September 2017.
- ▶ [WHO. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug resistant bacterial infections, including tuberculosis.](#) September 2017.

New WHO guidelines on antibiotic use in animals

Geneva – New WHO guidelines (1) recommend that farmers and the food industry should stop the routine use of antibiotics in healthy animals, except if a disease has been diagnosed in other animals in the same population. Where possible, sick animals should be tested to determine the most effective and prudent antibiotic to use, avoiding antibiotics classified as “highest priority critically important” for human health.

The new guidelines were informed by recent research that found that interventions restricting antibiotic use in food-producing animals reduced antibiotic-resistant bacteria in these animals by up to 39%.(2)

- ▶ [WHO News release, 7 November 2016.](#)
(1) [WHO guidelines on use of medically important antimicrobials in food-producing animals.](#) 2017.
- ▶ (2) [Tang KL *et al.* Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis.](#) *The Lancet Planetary Health* 2017; 1(8): e316-e327.

Website on antimicrobial susceptibility

United States of America – To enable health professionals to manage the use of antimicrobials better, the FDA has launched

a website that provides updated information about when bacterial or fungal infections are likely to respond to a specific medicine.

- ▶ [FDA-Recognized Antimicrobial Susceptibility Test Interpretive Criteria \[web page\].](#)

Antibiotic resistance in Australia

A recent report has revealed that antibiotic resistance in Australia is increasing and requires major efforts to control the spread of resistant strains. Despite some recent gains in efforts to encourage more careful use of antibiotics, as much as 56% of samples of enterococci can be resistant to vancomycin according to the report – a level higher than in any European country. Antibiotic use has been falling in Australian hospitals, but concerning levels of inappropriate prescribing remain both in hospitals and in the community. Methicillin-resistant *Staphylococcus aureus* (MRSA) has become the most common type of MRSA infection in the community and is now a more common cause of bloodstream infections than hospital-associated strains of MRSA. This is concerning, as no country has yet found effective interventions to control the spread of community-associated MRSA.

- ▶ [Antimicrobial Use and Resistance in Australia 2017 \(AURA 2017\): Second Australian report on antimicrobial use and resistance in human health.](#) 2 August 2017.

Antibiotic consumption

The seventh report of the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) shows that overall the sales of antibiotics for animal use decreased by 13% in Europe between 2011 and 2015, but that there are substantial differences between countries. A drop in sales of at least 5% was observed in 15 of the 25 countries that provided data for the full period. However, antibiotic sales increased by more than 5% in eight countries. Given

the substantial decline in the sales of antimicrobials for food-producing species in some countries, there is hope that decreases can also be achieved in others.(1) A new set of indicators will be used in the EU to assess Member States' progress in reducing antimicrobial resistance and antimicrobial consumption in both the human and animal sectors. The indicators are based on data gathered through existing EU monitoring networks and are presented in the form of a scientific opinion.(2)

In the United Kingdom, sales of antibiotics for use in animals fell to their lowest level since 1993. Sales of antibiotics that are critically important for humans accounted for less than 1% of all antibiotics sold for use in animals in 2016.(3)

In the U.S, antimicrobial sales for use in food-producing animals decreased for the first time in fifteen years. From 2015 to 2016 domestic sales and distribution of antimicrobials fell by 10% overall, and by 14% for medically important antimicrobials. These figures do not yet reflect changes in Guidance for Industry, which resulted in a voluntary transition of medically important antimicrobials used in the feed or water of food-producing animals from over-the-counter to either prescription or Veterinary Feed Directive marketing status, and withdrawal of all approved production indications (growth promotion and feed efficiency) for the affected products on 1 January 2017.(4)

- ▶ (1) EMA Press release 16 Oct 2017.
- (2) EMA News, 26 October 2017.
- (3) MHRA Press release, 27 October 2017.
- (4) FDA Releases Annual Summary Report on Antimicrobials Sold or Distributed in 2016 for Use in Food-Producing Animals. 7 December 2017.

Non-communicable diseases

Slow and uneven progress

Geneva – WHO has published its report on progress made by Member States to fight non-communicable disease (NCD). Heart and lung diseases, stroke, cancer and diabetes cause millions of untimely deaths before age 70 each year, of which 80% occur in low- and middle-income countries. The WHO *NCD Progress Monitor 2017* provides data on 19 indicators showing how countries build capacities to reduce and treat NCDs and how they address the four main risk factors: tobacco, unhealthy diet, physical inactivity and harmful use of alcohol.

The ten best-performing countries were Costa Rica and Iran (15 of 19 indicators achieved); Brazil, Bulgaria, Turkey and the United Kingdom (13 indicators achieved); and Finland, Norway, Saudi Arabia and Thailand (12 indicators achieved). But progress around the world has been uneven and insufficient to meet the Sustainable Development Goals target to reduce premature NCD deaths by one third by 2030. No country from the WHO Africa region achieved more than 8 of the 19 indicators; six achieved none of them.

The findings will underpin a WHO report that will be submitted to the United Nations Secretary General ahead of the third UN High-level Meeting on NCDs in 2018.

▶ [WHO News release, 18 September 2017.](#)

[WHO. Noncommunicable Diseases Progress Monitor 2017.](#)

New WHO high level commission

WHO will establish a new High-level global Commission on Noncommunicable Diseases to identify innovative ways to curb the world's biggest causes of death. The commission will support ongoing political efforts to prevent and treat cardiovascular

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disease, cancers, diabetes and respiratory disease and reduce suffering from mental health issues and the impact of violence and injuries. The announcement came ahead of the WHO Global Conference on Noncommunicable Diseases, co-hosted by WHO and the President of Uruguay.

► [WHO Statement, 10 October 2017.](#)

The Montevideo Roadmap

Montevideo – At the opening of the three-day Global Conference on Noncommunicable Diseases in Montevideo, hosted by WHO and the Presidency of Uruguay, governments endorsed the Montevideo Roadmap 2018–2030 on non-communicable diseases. The roadmap highlights the need for coordinated action from all sectors and the civil society to promote health and prevent and control NCDs. It also points out that most of the untimely deaths caused by NCDs – primarily heart and lung diseases, cancers and diabetes – could have been prevented by action against tobacco, air pollution, unhealthy diets, physical inactivity, and harmful use of alcohol, as well as by improved disease detection and treatment.

► [WHO News release, 18 October 2017.](#)

Tuberculosis

WHO Global Tuberculosis Report 2017

Geneva – WHO has released its Global Tuberculosis Report 2017. The findings show that progress is not on track to reach global targets. Tuberculosis remained the top infectious killer in 2016. It also caused the most deaths related to antimicrobial resistance and the most deaths among people with HIV.

In 2016, there were an estimated 10.4 million new tuberculosis cases

worldwide, 10% of which were among people living with HIV. Seven countries (India, Indonesia, China, Philippines, Pakistan, Nigeria and South Africa) accounted for 64% of the total burden. An estimated 1.7 million people died from tuberculosis. There were an estimated 490 000 new cases of multi-drug resistant tuberculosis, almost half of them in India, China and the Russian Federation.

Gaps in care and financing persist. Of the 10.4 million new cases, only 6.3 million were detected and officially notified in 2016. Only one in five patients with multi-drug resistant infections started treatment, and most people eligible for preventive tuberculosis treatment are not accessing it. Investments for tuberculosis care and prevention in low- and middle-income countries fall almost US\$ 2.3 billion short of the US\$ 9.2 billion needed in 2017. In addition, at least an extra US\$ 1.2 billion per year is required to accelerate the development of new vaccines, diagnostics, and medicines.

► [WHO News release, 30 October 2017.](#)

[WHO. Global Tuberculosis Report 2017.](#)

Ministerial Conference on Ending TB

Moscow/Geneva – At the WHO Global Ministerial Conference on Ending TB in the Sustainable Development Era, held in Moscow on 16–17 November 2017, 75 ministers agreed to take urgent action to end tuberculosis (TB) by 2030. The *Moscow Declaration to End TB* is a promise to increase multisectoral action, track progress and build accountability. More than 1000 participants took part in the two-day conference. Further commitments from heads of state will be sought at the first UN General Assembly High-Level Meeting on TB in 2018.

► [WHO News release, 17 November 2017.](#)

Hepatitis

São Paulo, Brazil – Over 900 delegates from 110 countries met at the World Hepatitis Summit 2017, held on 1–3 November 2017 in Brazil to discuss a common goal: the elimination of viral hepatitis. This biennial event is a joint initiative between the World Health Organization (WHO) and the World Hepatitis Alliance (WHA). The Summit closed with the launch of the São Paulo Declaration for a broad and coordinated approach to support implementation of WHO's Global Hepatitis Strategy.⁽¹⁾

Hepatitis causes more than 1.3 million deaths every year, and an estimated 328 million people are living with hepatitis, of which an estimated 71 million people have chronic hepatitis C infection. Despite some dramatic price reduction for new hepatitis C medicines, funding for key hepatitis services remains a major constraint in most countries. On the eve of the Summit WHO reported that close to 3 million people have accessed curative treatment for hepatitis C, and 2.8 million more embarked on lifelong treatment for hepatitis B in 2016. Hepatitis B infection rates in children under five have fallen due to better vaccine coverage. However the delivery of other prevention services remains low, leading to continuing rates of new infections including 1.75 million new hepatitis C cases every year. A functional cure for hepatitis B infection and more effective point-of-care diagnostics for hepatitis B and C need to be developed.⁽²⁾

► [WHO. World Hepatitis Summit 2017.](#)

[WHO News release, 31 October 2017.](#)

Polio

Geneva – The WHO Emergency Committee under the International Health Regulations (2005) (IHR) regarding the international spread of poliovirus

has unanimously agreed that the risk of international spread of poliovirus remains a Public Health Emergency of International Concern (PHEIC) and recommended the extension of revised Temporary Recommendations for a further three months.

In reaching this conclusion the Committee considered the potential risk of further spread of poliovirus through population movement particularly between Afghanistan and Pakistan, Nigeria and its Lake Chad neighbours, and countries bordering the Syrian Arab Republic, where a large outbreak is ongoing. The continued circulation of poliovirus in these countries demonstrates significant gaps in population immunity at a critical time in the polio endgame, when the world is closer to polio eradication than ever before in history. Following the global withdrawal of the type-2 component of oral poliovirus vaccine in April 2016, population immunity to type-2 polioviruses is rapidly waning. The global shortage of inactivated polio vaccine poses an additional risk. The Committee also noted with concern the recent detection of a single, highly diverged vaccine-derived type-2 poliovirus in sewage in Mogadishu, Somalia, with genetic evidence of more than three years of replication without detection.

► [WHO Statement, 14 November 2017.](#)

Cholera

Geneva – A new strategy to fight cholera has been launched by the Global Task Force on Cholera Control (GTFCC), a diverse network of more than 50 UN and international agencies, academic institutions and NGOs. The strategy aims to reduce cholera deaths by 90% by the year 2030 through early detection and response to outbreaks. By implementing the Roadmap,

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up to 20 countries could eliminate cholera by 2030.

Advances in water sanitation and hygiene have made Europe and North America cholera-free for several decades, and the introduction of oral cholera vaccine has bridged the gap between emergency response and longer-term control. However, cholera continues to kill an estimated 95 000 people annually and affects another 2.9 million, mostly in communities burdened by conflict, lack of infrastructure, poor health systems, and malnutrition. Protecting these communities before cholera strikes is more cost-effective than responding to outbreaks. Two WHO-prequalified oral cholera vaccines are now available and individuals can be fully vaccinated for just US\$6 per person, protecting them from the disease for up to three years.

► [WHO News release, 3 October 2017.](#)

Plague

Geneva – An unusually large outbreak of plague has been reported from Madagascar. In response WHO delivered nearly 1.2 million doses of antibiotics to health facilities and mobile clinics across the country. The Organization also released US\$1.5 million from its emergency funds to allow for immediate support until more substantial funds are received. WHO called for US\$5.5 million to respond to the outbreak.⁽¹⁾

In October, ten suspected cases reported from Seychelles tested negative for plague.⁽²⁾

Between 1 August and 22 November 2017 the Ministry of Public Health of Madagascar reported a total 2 348 cases of plague, including 202 deaths. By the end of November the outbreak had slowed down,

with a steady decline of new cases seen over several weeks. However, more infections of both bubonic and pneumonic plague are expected until the end of the plague season in April 2018.⁽³⁾

Plague is curable if treated early. It is endemic to Madagascar, where around 400 cases are reported annually. But this outbreak affected large urban areas, and more reported cases than usual were associated with pneumonic plague, which is more readily transmitted between patients than bubonic plague.

► ⁽¹⁾ [WHO News release, 6 October 2017.](#)

⁽²⁾ [WHO News release, 18 October 2017.](#)

⁽³⁾ [WHO News release, 27 November 2017.](#)

Marburg virus

Uganda – An outbreak of Marburg virus disease has occurred in eastern Uganda on the border with Kenya. The first confirmed case was detected by the Ministry of Health on 17 October 2017. An emergency response was initiated with support from WHO, the U.S. Centers for Disease Control and Prevention (CDC) and the African Field Epidemiology Network (AFNET). WHO deployed a rapid response team to the remote mountainous area and released US\$623 000 from its Contingency Fund for Emergencies. Health workers followed up with 316 close contacts of the patients in Uganda and Kenya. The outbreak, which claimed three lives, was successfully controlled only weeks after it was first detected.

Marburg virus disease is a rare and often fatal disease for which there is no specific treatment. It is caused by a virus from the same family as the Ebola virus. Transmission is by direct contact with the blood, body

fluids and tissues of infected persons or wild animals, for example monkeys and fruit bats.

► [WHO News release, 23 October 2017.](#)

[WHO News release, 8 December 2017.](#)

Yellow fever

Geneva – The International Coordinating Group (ICG) on vaccine provision for yellow fever has released 1.4 million vaccine doses to help control an outbreak in Nigeria. The first case was confirmed in August 2017; by 21 November 2017 a total 276 suspected cases had been reported in fourteen states of Nigeria.

The International Coordination Group (ICG) coordinates the timely and equitable provision of vaccines during outbreaks. Its members include the International Federation of Red Cross and Red Crescent Societies (IFRC), Médecins sans Frontières (MSF), the United Nations Children's Fund (UNICEF), and WHO. The ICG maintains an emergency stockpile of 6 million doses of yellow fever vaccine, funded by Gavi, the Vaccine Alliance. In 2017, nearly 6 million doses from the stockpile were deployed for emergency vaccination campaigns.

► [WHO News release, 1 December 2017.](#)

Diphtheria

Yemen – Diphtheria has made a comeback in war-torn Yemen, with 189 clinically diagnosed cases and 20 deaths – mostly children and young adults – in three months. WHO delivered 1000 vials of life-saving anti-toxins and 17 tonnes of medical supplies. Antibiotics and vaccines are also critical to treating and preventing the highly infectious respiratory disease; however both are in short supply in Yemen. WHO, UNICEF, and partners have worked with

available supplies, vaccinating 8 500 children under five years in two districts of the worst-affected governorate during November.

A vaccination campaign targeting 300 000 children younger than 12 months began on 25 November. Further vaccination rounds for more than 3 million children and young adults in priority districts are due in December.⁽¹⁾

Diphtheria is also rapidly spreading among Rohingya refugees in Cox's Bazar, Bangladesh. More than 110 suspected cases, including 6 deaths, have been clinically diagnosed. This could be just the tip of the iceberg in this extremely vulnerable population. WHO and partners have vaccinated more than 700 000 people against cholera and more than 350 000 children against measles and rubella. WHO has procured 1000 vials of anti-toxins to treat people that are already infected. A campaign targeting all children up to 6 years with pentavalent (DPT-HepB-Hib) and pneumococcal vaccines is in preparation.⁽²⁾

► ⁽¹⁾ [WHO News release, 27 November 2017.](#)

⁽²⁾ [WHO News release, 6 December 2017.](#)

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Prequalification

Stability data requirements

The WHO Prequalification Team – Medicines (PQT-m) has published updated information on minimum stability data required at the time of filing a generic product application.⁽¹⁾ Previously three months' stability data at the time of submission had been accepted for reproductive health and second-line anti-tuberculosis products as an interim exception to encourage the submission of poorly-represented products on the list of WHO-prequalified products. This exception has been re-evaluated, and it has been concluded that it is no longer needed.

The minimum stability requirements for all products at the time of submission to PQT-m are six months' accelerated and six months' long-term stability data. This is in line with the requirements of most major regulators.⁽²⁾

► ⁽¹⁾ WHO Prequalification News, 26 September 2017.

⁽²⁾ Regulatory collaboration. IGDPR generic drug product regulatory gap analysis. WHO Drug Information. 2016;30(3):361-369.

Presubmission meetings

The WHO Prequalification Team – medicines (PQT-m) has published detailed information about pre-submission meetings. These meetings provide an opportunity for advice and guidance prior to submission of a medicines dossier. They are compulsory for new applicants, and are useful for all applicants to address issues specific to their intended dossier.

► WHO Prequalification News, 3 November 2017.

Prequalified “Firsts”

- First praziquantel active pharmaceutical ingredient (API)
 - First generic dolutegravir tablets, for treatment of HIV
 - First linezolid API, for use in medicines to treat drug-resistant tuberculosis
 - First terizidone finished product, to treat drug-resistant tuberculosis
 - First entecavir finished product, to treat hepatitis C
- WHO prequalification website: <https://extranet.who.int/prequal/>
- First prequalified vector control product: SumiShield 50WG for use as an indoor residual spray. The product comes as a water-dispersible granule containing the active ingredient clothianidin.
- WHO. Prequalification Vector Control. Prequalified Lists [webpage].

Target product profile for rapid cholera tests

In order to treat cholera and quickly stem a potential outbreak, it is important to have a rapid and accurate diagnosis. Rapid diagnostic tests for cholera exist, but recent published evaluations show their accuracy is not optimal.

WHO has developed a target product profile describing the type of assays together with desired and acceptable key attributes. The target product profile provides a clear and tangible vision and focus for product development. Applications for prequalification assessment will be accepted as of 1 January 2018.

► WHO Essential medicines and health products. WHO outlines requirements for rapid cholera tests to prevent major outbreaks. 9 November 2017.

New essential medicines lists online

The updated WHO Model List of Essential Medicines for adults (EML) and WHO Model List of Essential Medicines for Children (EMLc) have been published in the WHO Technical Report Series, in replacement of the unedited version published in June 2017.

The 2017 report uses a new format that sets the stage for future developments. Available treatments – for example antibiotic and diabetes medicines – are presented for diseases or syndromes rather than individual medicines, facilitating broader comparisons and more selective listing.

The report has a new, user-friendly structure and layout. Concise, uniform summaries of the public health relevance, evidence of benefits and harms and the Committee's considerations and decisions are found in the body of the report. The table of content has clickable hyperlinks to each chapter and section. The EML, EMLc, the Anatomical Therapeutic Chemical (ATC) Classification System and an alphabetical list of essential medicines with ATC numbers are found in the annexes.

- ▶ WHO. The Selection and Use of Essential Medicines. [WHO Technical Report Series 1006, 2017.](#)

Outcomes of programme review

Resolution WHA68.18 requested WHO to commission a review of its global strategy and plan of action on public health, innovation and intellectual property. The independent review panel has now published its findings. The panel concluded that the eight elements of the strategy remain broadly valid, but that the actions for its implementation should be more focused.

Among the priority actions to improve access to health products the panel

recommended that WHO should continue to support Member States in strengthening regulatory capacity, regional harmonization and other collaborative initiatives, and that Member States and funders should support the WHO Prequalification of Medicines Programme to include newer essential health products. To promote more sustainable financing Member States should, among other things, encourage the implementation of schemes that partially or wholly delink product prices from research and development costs.

- ▶ WHO. Overall programme review of the global strategy and plan of action on public health, innovation and intellectual property [[web page](#)]. [Report of the review panel. November 2017.](#)

Framework for action against antimicrobial resistance

Over 100 country representatives and experts from the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE) and WHO met in Geneva, Switzerland on 9–10 November 2017 to discuss a future global framework for actions to achieve objectives 4 and 5 of the *Global action plan on antimicrobial resistance*.⁽¹⁾ The future global framework for development and stewardship to combat AMR aims to support research and development of new, affordable medicines, testing tools and vaccines, and to promote affordable access to new and existing antimicrobials along with stewardship policies for their appropriate use.

- ▶ [WHO Essential medicines and health products. News, 22 November 2017.](#)

⁽¹⁾ [Global action plan on antimicrobial resistance](#). ISBN: 9789241509763. Geneva: WHO, 2015.

WHO updates

WHO guidance on medicines quality

The Expert Committee for Specifications on Pharmaceutical Preparations oversees the maintenance of *The International Pharmacopoeia* (Ph. Int.) and provides guidance for use by relevant WHO units and regulatory authorities in WHO Member States. At its Fifty-Second Meeting, held in Geneva, Switzerland, on 16–20 October 2017, the Committee adopted the international guidance and good practices texts listed below, subject to their finalization as agreed at the meeting. The consultation versions of the texts are available at www.who.int/entity/medicines/areas/quality_safety/quality_assurance/projects.

For publication as annexes to the WHO Technical Report Series (2018):

- Considerations for requesting analysis of medicines samples (revision)
- WHO model certificate of analysis (revision)
- WHO guidance on testing of “suspect” falsified medicines
- WHO guidelines on good herbal processing practices (GHPP) for herbal medicines
- WHO good manufacturing practices for herbal medicines (maintenance)
- Good Pharmacopoeial Practices: Chapter on compounding¹
- Good Pharmacopoeial Practices: Chapter on monographs on herbal medicines¹
- Guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems (revision)
- Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical

practices for medical products regulatory decisions

- Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (revision)
- Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities

The Committee furthermore endorsed the proposed approach to conducting solubility studies for the purpose of revising the WHO biowaiver list.

For inclusion in *The International Pharmacopoeia*:

- General chapter on capillary electrophoresis

Monographs on antimalarials:

- Pyrimethamine (revision)
- Pyrimethamine tablets

Monographs on antiviral medicines, including antiretrovirals:

- Atazanavir sulfate (revision)
- Atazanavir capsules (revision)
- Efavirenz, emtricitabine and tenofovir disoproxil fumarate tablets (revision)
- Ganciclovir
- Ganciclovir for injection

Monographs on antituberculosis medicines:

- Capreomycin sulfate (revision)
- Capreomycin powder for injection (revision)
- Moxifloxacin hydrochloride
- Moxifloxacin tablets
- Protionamide (revision)
- Protionamide tablets

Monographs on anti-infectives:

- Amoxicillin trihydrate (revision)
- Clavulanate potassium
- Amoxicillin and clavulanic acid
- Clindamycin palmitate hydrochloride

¹ Subject to approval by the world pharmacopoeias in their final round of review

- Clindamycin palmitate powder for oral solution

Texts adopted for inclusion in *The International Pharmacopoeia* (*continued*)

Monographs on medicines for chronic diseases and for mental health:

- Atenolol (revision)
- Dacarbazine (revision)

Monographs on other medicines:

- Ciclosporin (revision)

In addition the Committee adopted alternative methods for the revision of the following 32 monographs that currently prescribe titrations using mercuric acetate: Amiloride HCl,² Amitriptyline HCl, Biperiden HCl, Chlorhexidine dihydrochloride, Chlorpromazine HCl, Dopamine HCl, Edrophonium chloride, Ephedrine HCl, Ethambutol HCl, Fluphenazine HCl, Homatropine hydrobromide, Homatropine methylbromide, Ketamine HCl, Lidocaine HCl, Loperamide HCl, Metoclopramide HCl, Morphine HCl, Naloxone HCl, Neostigmine bromide, Pilocarpine HCl, Procarbazine HCl, Proguanil HCl, Propranolol HCl, Pyridostigmine bromide, Pyridoxine HCl, Quinine dihydrochloride, Quinine HCl, Suxamethonium chloride, Tetracycline HCl, Thiamine hydrobromide, Thiamine HCl and Verapamil HCl.

The Committee adopted the following texts on radiopharmaceuticals, developed by the International Atomic Energy Agency (IAEA) in accordance with the agreed procedure:

- General monograph on radiopharmaceuticals (revision)

- Fludeoxyglucose (¹⁸F) injection (revision)
- Sodium pertechnetate (^{99m}Tc) injection (fission) (revision)
- Sodium pertechnetate (^{99m}Tc) injection (non-fission) (revision)
- Technetium (^{99m}Tc) bicsiate complex injection (revision)
- Technetium (^{99m}Tc) colloidal sulfur injection (revision)
- Technetium (^{99m}Tc) colloidal tin injection (revision)
- Technetium (^{99m}Tc) mebrofenin complex injection (revision)
- Technetium (^{99m}Tc) medronate complex injection (revision)
- Technetium (^{99m}Tc) mertiatide complex injection (revision)
- Technetium (^{99m}Tc) pentetate complex injection (revision)
- Technetium (^{99m}Tc) sestamibi complex injection (revision)
- Technetium (^{99m}Tc) succimer complex injection (revision)
- Technetium (^{99m}Tc) tetrofosmin complex injection (revision)
- Technetium (^{99m}Tc) tin pyrophosphate complex injection (revision)
- Gallium (⁶⁷Ga) citrate injection (revision)
- Iobenguane (¹²³I) injection (revision)
- Iobenguane (¹³¹I) injection (revision)
- Sodium (¹²⁵I) iothalamate injection (revision)
- Sodium iodide (¹³¹I) capsules (revision)
- Sodium phosphate (³²P) injection (revision)
- Samarium (¹⁵³Sm) leixidronam complex injection (revision)
- Strontium (⁸⁹Sr) chloride injection (revision)
- Yttrium (⁹⁰Y) silicate injection (revision)

² HCl = hydrochloride

Consultation documents

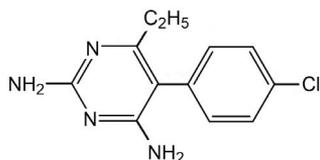
To receive draft monographs by email please contact Mrs Wendy Bonny (bonnyw@who.int), stating that you wish to be added to the electronic mailing list.

The International Pharmacopoeia

Pyrimethamine (Pyrimethaminum)

This is a draft proposal of a revised monograph for *The International Pharmacopoeia* (Working document QAS/17.696/Rev.2, November 2017). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

[*Note from the Secretariat: It is proposed to revise the monograph on Pyrimethamine in The International Pharmacopoeia.*]



$C_{12}H_{13}ClN_4$

Relative molecular mass. 248.7

Chemical name. 2,4-Diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine; 5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine; CAS Reg. No. 58-14-0

Description. A white, crystalline powder.

Solubility. Practically insoluble in water; slightly soluble in ethanol (~750 g/L) TS and acetone R.

Category. Antimalarial.

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

Additional information. Pyrimethamine exhibits polymorphism.

Requirements

Definition. Pyrimethamine contains not less than 99.0% and not more than 101.0% of $C_{12}H_{13}ClN_4$, calculated with reference to the dried substance.

Identity tests

- Either test A alone or tests B and C may be applied
- A. Carry out the examination as described under [1.7 Spectrophotometry in the infrared region](#). The infrared absorption spectrum is concordant with the spectrum obtained with pyrimethamine RS or with the reference spectrum of pyrimethamine.

If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the test substance and pyrimethamine RS in a small amount of dehydrated ethanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from pyrimethamine RS.
- B. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions given under the “Related Substances” with the following modifications. For solution (2) dissolve 12.5 mg pyrimethamine RS in about 20 mL solvent solution, sonicate for 10 minutes and dilute to 100.0 mL with mobile phase. Inject 30 μ L of solution (1) and (2). The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak corresponding to pyrimethamine in the chromatogram obtained with solution (2).
- C. The absorption spectrum ([1.6](#)) of a 15 μ g/mL solution in hydrochloric acid (0.005 mol/L) VS, when observed between 230 nm and 350 nm, exhibits a maximum at about 272 nm and a minimum at about 261 nm.

Sulfates. Shake 1.0 g with 50 mL of distilled water for 2 minutes and filter. Proceed with the filtrate as described under [2.2.2 Limit test for sulfates](#); the sulfate content is not more than 0.08 mg/g.

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

Loss on drying. Dry at 105°C for 4 hours; it loses not more than 5.0 mg/g.

Acidity or alkalinity. Boil 0.3 g with 15 mL of water, cool and filter. Add 0.25 mL of methyl red/ethanol TS to the filtrate; a yellow colour is observed. Not more than 0.1 mL of hydrochloric acid (0.05 mol/L) VS is required to change the colour of the solution to red.

Related substances. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (10 cm x 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3.5 μ m). The material contains embedded polar groups.¹

Prepare an ammonia solution by adding 10.0 mL of ammonia (~260 g/L) TS to 150 mL of water R, mix and dilute to 200.0 mL with water. Prepare an ammonium bicarbonate buffer pH 9.3 by dissolving 0.8 g of ammonium bicarbonate R in 1500 mL of water, adjust the pH to 9.3 by adding the ammonium solution (about 25 mL), mix and dilute to 2000.0 mL with water R.

¹ Waters Xbridge Shield RP18 has been found suitable.

Pyrimethamine (Ph. Int.)

As the mobile phase, use a mixture of 55 volumes of ammonium bicarbonate buffer pH 9.3 and 45 volumes of methanol R.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm. Maintain the column temperature at 35°C.

Prepare as a solvent solution a mixture of 50 volumes of acetic acid (~ 10 g/L) TS and 50 volumes of methanol R.

Prepare the following solutions. For solution (1) weigh 25 mg of pyrimethamine, accurately weighed, into a 20 mL volumetric flask. Add approximately 15 mL of the solvent solution and sonicate for about 10 minutes. Dilute to volume with the solvent solution solvent and mix. Dilute 5.0 mL of the filtrate to 50.0 mL with mobile phase. For solution (2) dilute 10.0 mL of solution (1) to 100.0 mL with mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase. For solution (3) prepare 20 mL of a 1.25 mg/mL solution of pyrimethamine in sulfuric acid (~570 g/L) TS in a 25 mL conical flask. Heat the solution on a hotplate until it boils. Continue to heat to reduce the volume to about half its initial volume. The final solution should be clear with a light tinge of yellow. Cool and dilute 1 volume of this solution to 10 volumes with mobile phase.

Inject 30 µL of solution (3).

Record the chromatogram for about 2 times the retention time of pyrimethamine (retention time about 7 minutes). The impurities are eluted, if present, at the following relative retention with reference to the pyrimethamine: impurity A about 0.41; impurity B about 0.53 and impurity C about 0.69. The test is not valid unless in the chromatogram obtained with solution (3) the resolutions between impurities A and B is at least 3.0.

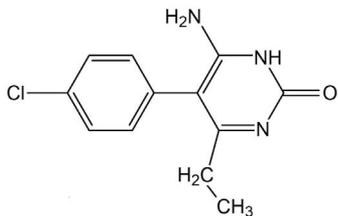
Inject alternately 30 µL of solution (1) and (2).

Use the chromatogram obtained with solution (3) to identify the peaks due to the impurities A, B and C.

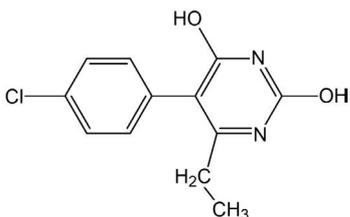
In the chromatogram obtained with solution (1):

- the area of any peak corresponding to either impurity A, B or C is not greater than 2.5 times the area of the peak due to pyrimethamine in the chromatogram obtained with solution (2) (0.25%);
- the area of any other impurity peak is not greater than the area of the peak due to pyrimethamine in the chromatogram obtained with solution (2) (0.10%);
- the sum of the areas of all impurities is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%). Disregard the peak due to pyrimethamine with an area less than 0.5 times the area of the principal peak obtained with solution (2) (0.05%).

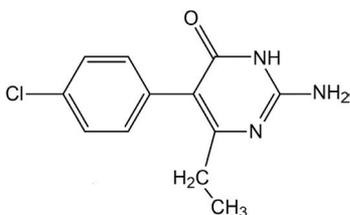
Assay. Dissolve about 0.40 g, accurately weighed, in 30 mL of anhydrous acetic acid R, heating gently. Cool and titrate with 0.1 M perchloric acid, determining the end-point potentiometrically. Each mL of 0.1 M perchloric acid is equivalent to 24.87 mg of $C_{12}H_{13}ClN_4$.

Impurities

- A. 4-amino-5-(4-chlorophenyl)-6-ethylpyrimidin-2(3H)-one (degradation product)



- B. 2,4-dihydroxy-5-(4-chlorophenyl)-6-ethylpyrimidine (degradation product)



- C. 2-amino-5-(4-chlorophenyl)-6-ethylpyrimidin-4(3H)-one (degradation product)

Reagents to be included:**Ammonium bicarbonate R**

Analytical reagent grade of commerce containing not less than 99% of NH₄HCO₃.

Pyrimethamine tablets (*Pyrimethamini compressi*)

This is a draft proposal of a monograph for *The International Pharmacopoeia* (Working document QAS/17.697/Rev.2, November 2017). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

[*Note from the Secretariat: It is proposed to include the monograph on Pyrimethamine tablets in The International Pharmacopoeia.*]

Category. Antimalarial.

Storage. Pyrimethamine tablets should be kept in a well-closed container, protected from light.

Additional information. Strengths in the current WHO Model List of Essential Medicines (EML): 25 mg. Strength in the current WHO EML for children: 25 mg.

Requirements

Comply with the monograph for [Tablets](#).

Definition. Pyrimethamine tablets contain not less than 90.0% and not more than 110.0% of the labelled amount of pyrimethamine (C₁₂H₁₃ClN₄).

Identity tests

- Either test A or tests B and C may be applied.
- A. Shake a quantity of the powdered tablets, containing about 50 mg of pyrimethamine, with 50 mL of dehydrated ethanol R for 20 minutes, filter and evaporate the filtrate to dryness. Carry out the examination as described under [1.7 Spectrophotometry in the infrared region](#). The infrared absorption spectrum is concordant with the spectrum obtained from pyrimethamine RS treated similarly.
- B. To a quantity of the powdered tablets, containing about 25 mg of pyrimethamine, add 50 mL of hot hydrochloric acid (~3.65 g/L) TS and heat on a water bath for 10 minutes, swirling occasionally. Mix with the aid of ultrasound for 30 minutes and cool to room temperature. Add sufficient hydrochloric acid (~3.65 g/L) TS to produce 100 mL. Filter a portion of this solution and discard the first few mL of the filtrate. Dilute 5 mL of the filtrate to 100 mL with hydrochloric acid (~3.65 g/L) TS. The absorption spectrum of the solution, when observed between 250 and 300 nm, exhibits a maximum at about 272 nm and a minimum at about 261 nm.
- C. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions given under “Assay”. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the peak due to pyrimethamine in the chromatogram obtained with solution (2).

Pyrimethamine tablets (Ph. Int.)

Dissolution. Carry out the test described under [5.5 Dissolution test for solid oral dosage forms](#) using as the dissolution medium 900 mL of hydrochloric acid (~3.65 g/L) TS and rotating the paddle at 50 revolutions per minute. At 45 minutes withdraw a sample of 10 mL of the medium through an in-line filter. Measure the absorbance ([1.6](#)) of a 1 cm layer of the filtered sample at the maximum at about 272 nm, using the dissolution buffer as the blank. Measure at the same time and under the same conditions the absorbance of a suitable solution of pyrimethamine RS in dissolution medium.

For each of the tablets tested, calculate the total amount of pyrimethamine ($C_{12}H_{13}ClN_4$) in the medium from the results obtained. The amount in solution for each tablet is not less than 75% (Q) of the amount declared on the label.

[Note from the Secretariat: It is intended to determine the absorptivity value of pyrimethamine during the establishment of pyrimethamine RS and to use this value for the calculation of the test result.]

Related substances. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions given under “Assay” with the following modifications:

For solution (2) dilute 10.0 mL of solution (1) to 100.0 mL with mobile phase. Dilute 1.0 mL of this solution to 100.0 mL with mobile phase. For solution (3) prepare 20 mL of a 1.25 mg/mL solution of pyrimethamine in sulfuric acid (~570 g/L) TS in a 25 mL conical flask. Heat the solution on a hotplate until it boils. Continue to heat to reduce the volume to about half its original volume. The final solution should be clear with a light tinge of yellow. Cool and dilute 1 volume of this solution to 10 volumes with mobile phase.

Inject 30 μ L of solution (3). Record the chromatogram for about 2 times the retention time of pyrimethamine (retention time about 7 minutes). The impurities are eluted at the following relative retention with reference to the pyrimethamine: impurity A about 0.41; impurity B about 0.53 and impurity C about 0.69. The test is not valid unless in the chromatogram obtained with solution (3) the resolutions between impurities A and B is at least 3.0.

Inject alternately 30 μ L of solution (1) and (2).

Use the chromatogram obtained with solution (3) to identify the peaks due to the impurities A, B and C.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to either impurity A, B or C is not greater than 2.5 times the area of the peak due to pyrimethamine in the chromatogram obtained with solution (2) (0.25%).

Assay. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (10 cm x 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3.5 μ m). The material contains embedded polar groups.¹

Prepare an ammonia solution by adding 10.0 mL of ammonia (~260 g/L) TS to 150 mL of water R, mix and dilute to 200.0 mL with water. Prepare the ammonium bicarbonate buffer pH

¹ Waters Xbridge Shield RP18 has been found suitable.

Pyrimethamine tablets (Ph. Int.)

9.3 by dissolving 0.8 g of ammonium bicarbonate R in 1500 mL of water, adjust the pH to 9.3 by adding the ammonium solution (about 25 mL), mix and dilute to 2000.0 mL with water R.

As the mobile phase, use a mixture of 55 volumes of ammonium bicarbonate buffer pH 9.3 and 45 volumes of methanol R.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm. Maintain the column temperature at 35°C.

Prepare as a solvent solution a mixture of 50 volumes of acetic acid (~ 10 g/L) TS and 50 volumes of methanol R.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity to the powdered tablets, containing about 125 mg of pyrimethamine, accurately weighed, into a 100 mL volumetric flask. Add approximately 75 mL of the solvent solution and sonicate for about 10 minutes. Dilute to volume with the solvent solution, mix and filter. Dilute 5.0 mL of the filtrate to 50.0 mL with mobile phase. For solution (2) dissolve 12.5 mg pyrimethamine RS in 20 mL, sonicate for 10 minutes and dilute to 100.0 mL with mobile phase.

Inject 30 µL of solution (1) and (2). Measure the areas of the peaks corresponding to pyrimethamine obtained in the chromatograms from solution (1) and (2) and calculate the percentage content of $C_{12}H_{13}ClN_4$ in the tablets, using the declared content of $C_{12}H_{13}ClN_4$ in pyrimethamine RS.

Impurities

The impurities limited by the requirements of this monograph include impurities A, B and C listed in the monograph on Pyrimethamine.

Reagents to be included:**Ammonium bicarbonate R**

Analytical reagent grade of commerce containing not less than 99% of NH_4HCO_3 .

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 2017. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology before 1 February 2018. If no objections are received before this date, the new ATC codes and DDDs will be considered final and included in the **January 2019 version of the ATC/DDD Index**.

New ATC 5th level codes

ATC level name/INN	ATC code
ambrisentan and tadalafil	C02KX52
atazanavir and ritonavir	J05AR23
atezolizumab	L01XC32
avelumab	L01XC31
caplacizumab	B01AX07
cefteram	J01DD18
cladribine ¹	L04AA40
clenbuterol and ambroxol	R03CC63
crisaborole	D11AH06
crofelemer	A07XA06
cytarabine and daunorubicin	L01XY01
dacomitinib	L01XE47
dapivirine	G01AX17
delafloxacin	J01MA23
doxepin	D04AX01
emapalumab	L04AA39
enasidenib	L01XX59
encorafenib	L01XE46

Continued

Temporary

New ATC 5th level codes (continued)

ATC level name/INN	ATC code
enisamium iodide	J05AX17
epacadostat	L01XX58
eravacycline	J01AA13
ertugliflozin	A10BK04
fexapotide	G04CX04
floxuridine	L01BC09
galcanezumab	N02CX08
glecaprevir and pibrentasvir	J05AP57
ibandronic acid and colecalciferol	M05BB09
icotinib	L01XE48
imidazolyl ethanamide pentandioic acid	J05AX21
indocyanine green	V04CX01
ipragliflozin	A10BK05
isoniazid, sulfamethoxazole, trimethoprim and pyridoxine	J04AM08
kagocel	J05AX22
lanadelumab	B06AC05
letermovir	J05AX18
lorlatinib	L01XE44
lusutrombopag	B02BX07
medroxyprogesterone and estradiol	G03AA17
meropenem and vaborbactam	J01DH52
metformin and ertugliflozin	A10BD23
naldemedine	A06AH05
neratinib	L01XE45
norgestimate and ethinylestradiol	G03AB09
ozanimod	L04AA38
patisiran	N07XX12
peramivir	J05AH03
riboflavin	S01XA26
rifampicin, ethambutol and isoniazid	J04AM07
roxadustat	B03XA05
sitagliptin and ertugliflozin	A10BD24
tebipenem pivoxil	J01DH06
telotristat	A07XA05
tildrakizumab	L04AC17
tilorone	J05AX19
tosufloxacin	J01MA22
uramustine	L01AD08
vaginal ring with progestogen	G02BB02
valbenazine	N07XX13
valsartan and nebivolol	C09DX05

- 1 Oral formulations indicated for multiple sclerosis.
Parenteral formulations are classified in L01BB04.

Temporary

Change of ATC level name

Previous	New	ATC code
dinutuximab	dinutuximab beta	L01XC16

New DDDs

ATC level name/INN	DDD	unit	Adm.R*	ATC code
atazanavir and ritonavir	0.3	g ¹	O	J05AR23
baricitinib	4	mg	O	L04AA37
cariprazine	3	mg	O	N05AX15
cefroxadine	2.1	g	O	J01DB11
cefteram	0.4	g	O	J01DD18
ceftriaxone and beta-lactamase inhibitor	2	g ²	P	J01DD63
colistin	9	MU	O	A07AA10
delafloxacin	0.9	g	O	J01MA23
delafloxacin	0.6	g	P	J01MA23
delamanid	0.2	g	O	J04AK06
desfesoterodine	3.5	mg	O	G04BD13
droxidopa	1	g	O	C01CA27
eluxadoline	0.2	g	O	A07DA06
enisamium iodide	1.5	g	O	J05AX17
estradiol	1.53	mg	TD spray	G03CA03
faropenem	0.75	g	O	J01DI03
follitropin delta	12	mcg	P	G03GA10
garenoxacin	0.4	g	O	J01MA19
gemifloxacin	0.32	g	O	J01MA15
imidazolyl ethanamide pentandioic acid	90	mg	O	J05AX21
insulin glargine and lixisenatide	40	U ³	P	A10AE54
kagocel	60	mg	O	J05AX22
kanamycin	3	g	O	A07AA08
lomefloxacin	0.4	g	O	J01MA07
mepyramine theophyllinacetate	0.6	g	O	R03DA12
midecamycin	1.2	g	O	J01FA03
misoprostol	0.2	mg	O	G02AD06
naldemedine	0.2	mg	O	A06AH05
nusinersen	0.1	mg	P	M09AX07
patiromer calcium	16.8	g	O	V03AE09
pyrimethamine, combinations	75	mg ⁴	P	P01BD51
reslizumab	7.1	mg	P	R03DX08
rimantadine	0.2	g	O	J05AC02
sarilumab	14.3	mg	P	L04AC14
secnidazole	2	g	O	P01AB07

Continued

Temporary

New DDDs (continued)

ATC level name/INN	DDD	unit	Adm.R*	ATC code
tebipenem pivoxil	0.56	g	O	J01DH06
thyroid gland preparations	0.1	g	O	H03AA05
tilorone	0.125	g	O	J05AX19
tosufloxacin	0.45	g	O	J01MA22

* Administration Route: O=oral; P=parenteral.

- 1** refers to atazanavir.
- 2** refers to ceftriaxone.
- 3** refers to insulin glargine.
- 4** refers to pyrimethamine.

Changes of DDDs

ATC level name/INN	Previous DDD			New DDD			ATC code
	DDD	Unit	Adm.R.*	DDD	Unit	Adm.R.*	
amoxicillin	1	g	O	1.5	g	O	J01CA04
amoxicillin	1	g	P	3	g	P	J01CA04
amoxicillin and beta-lactamase inhibitor ¹	1	g	O	1.5	g	O	J01CR02
ampicillin	2	g	P	6	g	P	J01CA01
cefepime	2	g	P	4	g	P	J01DE01
ciprofloxacin	0.5	g	P	0.8	g	P	J01MA02
colistin	3	MU	P	9	MU	P	J01XB01
meropenem	2	g	P	3	g	P	J01DH02

* Administration Route: O=oral; P=parenteral.

- 1** New ATC level name valid from 2018.

WHO Collaborating Centre for Drug Statistics Methodology
Oslo, November 2017

ATC/DDD classification (final)

The following ATC codes and DDDs were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in March 2017. These are considered final and included in the **January 2018 version of the ATC/DDD Index**.

New ATC 5th level codes

ATC level name/INN	ATC code
andexanet alfa	V03AB38
atorvastatin and perindopril	C10BX15
cenegermin	S01XA24
colecalfiferol, combinations	A11CC55
cytisine	N07BA04
dolutegravir and rilpivirine	J05AR21
durvalumab	L01XC28
emicizumab	B02BX06
emtricitabine, tenofovir alafenamide and bictegravir	J05AR20
emtricitabine, tenofovir alafenamide, darunavir and cobicistat	J05AR22
erenumab	N02CX07
ermekumab	L01XC29
evogliptin	A10BH07
fimasartan and diuretics	C09DA10
formoterol, glycopyrronium bromide and beclometasone	R03AL09
guselkumab	L04AC16
ivacaftor and tezacaftor	R07AX31
lifitegrast	S01XA25
metformin and evogliptin	A10BD22
nusinersen	M09AX07
oxycodone and naltrexone	N02AA56
plecanatide	A06AX07
polmacoxib	M01AH07
ropeginterferon alfa-2b	L03AB15
sirukumab	L04AC15
sofosbuvir, velpatasvir and voxilaprevir	J05AP56
tavorole	D01AE24
vestronidase alfa	A16AB18
vilanterol, umeclidinium bromide and fluticasone furoate	R03AL08

Final

Changes of ATC level names

Previous	New	ATC code
Adrenergics in combinations with anticholinergics	Adrenergics in combinations with anticholinergics incl. triple combinations with corticosteroids ¹	R03AL
eptacog alfa	coagulation factor VIIa	B02BD08

¹ Decided at the October 2017 meeting of the WHO International Working Group for Drug Statistics Methodology. To be implemented in the 2018 version of the ATC/DDD index.

New DDDs

ATC level name/INN	DDD	unit	Adm.R*	ATC code
brexpiprazole	3	mg	O	N05AX16
cyclizine	0.1	g	P	R06AE03
etelcalcetide	2.1	mg	P	H05BX04
evogliptin	5	mg	O	A10BH07
ixekizumab	2.9	mg	P	L04AC13
levomethadone	15	mg	O	N07BC05
methotrexate	2.5	mg	P	L04AX03
obeticholic acid	10	mg	O	A05AA04
plecanatide	3	mg	O	A06AX07
tenofovir alafenamide	25	mg	O	J05AF13

* Administration Route: O=oral; P=parenteral.

Change of DDD

ATC level name/INN	Previous DDD			New DDD			ATC code
	DDD	Unit	Adm.R.*	DDD	Unit	Adm.R.*	
glycopyrronium bromide	3	mg	P	0.3	mg	P	A03AB02

* Administration Route: P=parenteral.

WHO Collaborating Centre for Drug Statistics Methodology
Oslo, November 2017