## WHO Drug Information

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ATC/DDD classification

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

International Nonproprietary Names (INN)

Proposed INN: List 115

Abbreviations and web sites

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

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

International Conference of Drug Regulatory Authorities (ICDRA) comes to Africa

Established in 1980 as a platform to develop international consensus, the WHO-convened ICDRA conference has become the place of choice for regulators from WHO Member States to meet and discuss strategies to harmonize regulation and improve the safety, efficacy and quality of medicines. The 17th ICDRA, to be held in November 2016, will be the first to take place in sub-Saharan Africa.

ICDRA – a forum for regulatory authorities
The International Conference of Drug Regulatory Authorities (ICDRA) provides medical products regulators of WHO Member States with a forum to meet and discuss ways to strengthen collaboration. It is co-organized every two years by WHO and the regulatory authority of the host country.

The ICDRA conferences have been guiding regulatory authorities, WHO and interested stakeholders in determining priorities for action in national and international regulation of medicines, vaccines, biomedicines and herbal products. The ICDRA programme is developed by a planning committee of representatives from medicines regulatory authorities. While the pre-ICDRA event is open to all interested stakeholders, participation at the actual conference is restricted to representatives of medicines regulatory authorities. Recommendations are agreed at each ICDRA for action among agencies, WHO and related institutions and are documented on the WHO web site (1).

International Conference of Drug Regulatory Authorities (ICDRA)
The 17th ICDRA will take place in Cape Town, South Africa on 27 November – 2 December 2016

Register now:
www.icdra.co.za
Closing date for registrations: 31 August 2016
Bringing regulators together
From their inception, the ICDRA conferences have been instrumental in bringing regulators together to move towards international harmonization (Box 1). Regulatory harmonization was pioneered in Europe some forty years ago, eventually leading to the establishment of the International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH, recently renamed International Council on Harmonization)\(^1\). Regulatory harmonization then took hold in other parts of the world, with active initiatives ongoing within the Pan American Network for Drug Regulatory Harmonization (PANDRH), the Asia-Pacific Economic Cooperation (APEC), the Association of the Southeast Asian Nations (ASEAN), the Gulf Cooperation Council (GCC) and more recently also in Africa.

Focus on Africa
The potential benefits of harmonizing medicines registration in Africa were recognized at the 13th ICDRA in 2008. A WHO concept paper was then developed to describe a proposed approach to supporting harmonization of medicines registration within and across African regional economic communities (2). Further discussions and a call for proposals followed in 2009. The first project started in the East African Community (EAC) in 2011; active projects are meanwhile ongoing in several regions.

One aim of the African Medicines Regulatory Harmonisation Programme (AMRH) is to establish – in partnership with the African Union Commission and WHO – the African Medicines Agency, which will operate under the authority of AMRH. During a meeting in Luanda in 2014, African Health Ministers endorsed this proposal (3).

Given this impressive momentum, it is fitting that in 2016 the ICDRA conference should come to Africa. The 17th ICDRA will be hosted by the South African medicines regulatory authority in Cape Town on 29 November – 2 December 2016. The theme of the event is “Patients are waiting: How regulators collectively make a difference”. In keeping with

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\(^1\) www.ich.org

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**Box 1: ICDRAs around the world**

| 1st ICDRA | 2nd ICDRA | 3rd ICDRA | 4th ICDRA | 5th ICDRA | 6th ICDRA | 7th ICDRA | 8th ICDRA | 9th ICDRA | 10th ICDRA | 11th ICDRA | 12th ICDRA | 13th ICDRA | 14th ICDRA | 15th ICDRA | 16th ICDRA | 17th ICDRA |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Annapolis (United States of America) | Rome (Italy) | Saltsjöbaden (Sweden) | Tokyo (Japan) | – first in Asia | Paris (France) | Ottawa (Canada) | Noordwijk (Netherlands) | Manama (Bahrain) | – first in an Arabic country | Berlin (Germany) | Hong Kong (China) | Madrid (Spain) | Seoul (Republic of Korea) | Berne (Switzerland) | Singapore (Singapore) | Tallinn (Estonia) | Rio de Janeiro (Brazil) | – first in South America | Cape Town (South Africa) | – first in Africa |
the motto of “Strengthening regulatory systems through convergence, reliance and networks” the 17th ICDRA offers a rich programme of topics for discussion (Box 2).

More than ever, regulatory convergence and cooperation are needed to ensure that patients around the world, including those in the resource-constrained environments of many African countries, have access to quality medical products at affordable prices. By facilitating discussions among regulators in an atmosphere of trust and professional commitment, the 17th ICDRA will be instrumental in bringing about progress in this ambitious agenda. It is an opportunity not to be missed by any regulatory authority wishing to contribute to global regulatory convergence, effective collaboration and good regulatory practices in the interest of public health.

References

(See page 229 under “Upcoming events” for practical information)
Quality testing of vaccines

Hands-on training on a standardized protocol to test saccharide content of priority vaccines

To facilitate access to good-quality vaccines, the WHO Prequalification Team (PQT) promotes standardized testing protocols that can be used to test vaccines produced by different manufacturers. A harmonized test method has been identified to determine polyribosyl-ribitol-phosphate (PRP) content in liquid vaccine combinations containing a whole-cell pertussis component. The use of this method saves significant time and resources at quality control laboratories. Hands-on training courses for quality control laboratory technicians from 13 countries have been organized, enabling them to implement this protocol at their institutions.

Introduction

Diphtheria, tetanus, whole-cell pertussis (DTwP)-based pentavalent vaccine (liquid presentation) is a globally important vaccine. This combination “five-in-one” vaccine protects children from diphtheria, pertussis (whooping cough), tetanus, hepatitis B and Haemophilus influenzae type b (Hib), which causes pneumonia and meningitis. It is less traumatic for infants to receive and easier for programmes to administer than previous formulations. In recent years, global demand for this vaccine has increased rapidly (1). The WHO Prequalification Team (PQT) prequalifies this type of vaccine for use in national immunization programmes (2).

The active ingredient of a Hib vaccine that prevents infection by H. influenzae type b is polyribosyl-ribitol-phosphate (PRP), a saccharide. Total and free (unconjugated) saccharide content is the single critical parameter indicative of Hib conjugate vaccine quality. However, quantitative determination of PRP in different liquid formulations is challenging for laboratories and manufacturers because differences in Hib carrier protein, antigen combinations, adjuvant, preservatives and other excipients interfere with the testing. Specific methodologies need to be established and validated for each individual product, which is time-consuming. Laboratories that test Hib vaccines on behalf of WHO PQT during the prequalification process usually use their own testing methods, since applying the manufacturer’s methodology

The content of this article was contributed by Dr Ute Rosskopf of the WHO Prequalification Team. The study to identify a harmonized assay was organized in the framework of the WHO Vaccines Prequalification Programme, with funding from the United States Agency for International Development (USAID). WHO thanks Dr Christina von Hunolstein, Bacterial Vaccine Unit, National Centre for Immunobiologicals Research and Evaluation (CRIVIB), Istituto Superiore di Sanità (ISS), Italy, and Dr Barbara Bolgiano, Division of Bacteriology, National Institute of Biological Standards and Control (NIBSC), United Kingdom, for performing the tests in the study and co-organizing the subsequent hands-on training courses. WHO is grateful to the following manufacturers for their donations of vaccine samples (in alphabetical order): Berna Biotech Korea Corp., Yeonsu-gu, Incheon, Republic of Korea; Biological E. Limited, Hyderabad, India; Novartis Vaccines and Diagnostics S.r.l., Siena, Italy; Serum Institute of India Limited, Hadapsar, Pune, India. The preparation of a pentavalent vaccine exclusively for the purpose of this study was much appreciated.
would take even more time and would represent an additional challenge.

**A harmonized assay**

During evaluation of a new product for prequalification, a WHO-contracted laboratory obtained non-compliant results when testing the PRP content of the Hib component of a pentavalent vaccine lot. A group of experts convened by WHO concluded that the non-compliance was due to differences in testing methodologies rather than a deficiency in the product itself. The experts recommended that WHO focus on standardization of a test protocol to assess PRP in liquid vaccine preparations.

In 2013 WHO PQT initiated a small project to identify a protocol to reliably determine the total and free PRP content of the Hib conjugate component of liquid vaccine presentations (3). Two laboratories were requested to test samples of five selected vaccines according to their own test protocols, using two different reference standards. The data demonstrated that one of the protocols was successful in providing accurate measurements of total and unconjugated PRP in complex matrices of immunogens, adjuvants and excipients (Box 1).

The test protocol identified in the study gives laboratories an efficient means of determining Hib component in liquid vaccine presentations produced by different manufacturers. Additional investigations showed that the test protocol is applicable to all WHO-prequalified vaccine combinations containing a whole-cell pertussis component (5) – which is used in most developing countries consistent with WHO recommendations (6) – using either of the two reference standards.

To verify the method further, another study was subsequently conducted in collaboration with the Biological Standardisation Programme of the European Directorate for the Quality of Medicines & HealthCare (EDQM) and the EU Commission, with participation of five manufacturers and five national control laboratories. Publication of the results is under way.

**Hands-on training courses**

*Testing of Hib-combination vaccines*

To support countries in quality assurance for Hib-containing liquid combination vaccines, a hands-on training course was designed to enable correct implementation of the assay identified in the study. The trainees perform sample preparation and other critical steps for the chromatographic runs, and calculate their own test results using a dedicated Excel spreadsheet. Test outcomes, real-life experiences and challenges in using the test protocol are discussed extensively.

During 2014 and 2015 four one-week courses were co-organized by WHO and the Bacterial Vaccine Unit of the Istituto Superiore di Sanità (ISS) in Rome, Italy. A total of 20 participants were trained, including four from India, three from the Republic of Korea, two each from Cuba and Indonesia and one each from Bangladesh, Brazil, Canada, China, Iran, Mexico, Poland, South Africa and Thailand. A fifth course will take place in June 2016 at the national control laboratory in China.

Feedback from course participants has been extremely positive. Suggestions were made for WHO to offer similar training on other glycoconjugated or polysaccharide vaccines, as well as additional theoretical training on issues such as validation of High Performance
Box 1: Identification of a harmonized assay

**Study aim:** To compare total and free polyribosyl-ribitol-phosphate (PRP) content of the *H. influenzae* type b conjugate component of liquid vaccine presentations as determined at two independent laboratories with the values obtained by the manufacturer at lot release.

**Materials and methods:** High-performance anion exchange chromatography pulsed amperometric detection (HPAEC-PAD) (4) was performed at two laboratories using their own HPAEC-PAD protocols and validity criteria.

Vaccine sample panel (the order does not reflect the sample numbers in the Figures below):
- DTPwHepB-Hib: Hib-TT, Thiomersal (0.01 %), Al phosphate
- DTPwHepB-Hib: Hib-TT, Thiomersal (0.005 %), Al phosphate
- DTPwHepB-Hib: Hib-CRM, Al phosphate
- DTPw-Hib: Hib-CRM, Thiomersal, Al phosphate
- DTPwHepB-Hib: Thiomersal, Al phosphate, sub-potent Hib-TT component (low total PRP content and high free PRP content) prepared for the purpose of the study.

Reference standards (RS):
- Ribitol RS (Fluka, lot number BCBJ6567V).
- WHO PRP 1st International Standard (code no. 02/208).

Analytical conditions:
Samples were analyzed as described in the laboratories’ HPAEC-PAD test protocols. A Dionex DX-500 chromatography system equipped with a CarboPac MA1 analytical column was used in combination with a CarboPac MA1 guard column. PRP was hydrolyzed with 0.3 M HCl for 2 hours at 100°C. Samples were pre-treated to determine free PRP content, using C4 SPE cartridges (Laboratory 1) or 30 or 100 kDa pore size Microcon ultrafiltration membranes (Laboratory 2). Two independent runs were performed to determine total and free PRP content.

**Results:** Figures 1 and 2 show the total and free PRP content determined by the manufacturer at lot release (Mf) and the geometrical means of the two values obtained at each of the two laboratories (Lab1, Lab2).

**Figure 1:** Total PRP content (µg per single human dose)

**Figure 2:** Free PRP content (percentage per single human dose)

**Conclusions**
- Both laboratories identified the sub-potent vaccine (Sample 5).
- The two reference standards gave similar results at both laboratories.
- The test protocol of Laboratory 1 showed better agreement with the manufacturers’ data for the free PRP content than the test protocol of Laboratory 2.
Quality testing of vaccines

Anion Exchange Chromatography with Pulsed Amperometric Detection (HPAEC-PAD) analysis, statistical analysis, creation of validity criteria and qualification of chromatographic equipment.

Testing of meningococcal vaccines

Course participants had expressed interest in trainings on meningococcal vaccines, which – like Hib combination vaccines – are on the priority list for WHO prequalification (7). In February 2016 WHO and the Division of Bacteriology of the U.K. National Institute of Biological Standards and Control (NIBSC) organized a two-week course on the use of HPAEC-PAD for the quantitative determination of the saccharide content of the meningococcal serotypes A, C, W and Y. Participants from the national control laboratories of Brazil, China, Cuba, India, Indonesia and South Africa attended the training.

Conclusions

The harmonized assay for testing of saccharide content in liquid combination vaccine preparations enables national quality control laboratories and manufacturers to reduce the time spent on developing and transferring test methods.

There are currently eight liquid Hib combination vaccines with a whole cell pertussis component on the WHO prequalification list (5), originating from Italy, the Republic of Korea, India and Indonesia. Technicians from these and ten additional countries participated in hands-on training courses on the use of the harmonized test protocol. Training on HPAEC-PAD testing of meningococcal vaccines has also started. Further courses will follow.

Successful implementation of the harmonized assay, based on proper validation, will enable quality control laboratories to obtain accurate and reliable testing outcomes. This will benefit the prequalification process and thereby help to ensure a sustainable supply of good quality vaccines to national immunization programmes. Considering that immunization is one of the most cost-effective public health interventions (8), the value for WHO Member States is significant.

References

5 WHO. WHO prequalified vaccines_list of prequalified vaccines [web page]. Available at: https://extranet.who.int/gavi/PQ_Web/
Medicines shortages

Global approaches to addressing shortages of essential medicines in health systems

Shortages of essential drugs are becoming increasingly frequent globally, burdening health systems with additional costs and posing risks to the health of patients who fail to receive the medicines they need.

The problem has received increasing attention in recent years. Building on the outcomes of previous discussions, participants at a WHO-convened technical consultation reviewed the factors contributing to medicines shortages and discussed approaches that could be effective to prevent and manage them at the global scale.

Background

Shortages of essential medicines have been reported from high-, middle- and low-income countries. They are expensive for health systems to manage, causing additional costs for replacement of medicines and absorbing significant staff time (Box 1). Medicines shortages pose risks for patient health as a result of non-treatment, under-treatment and possible medication errors from attempts to substitute missing medicines.

While medicines shortages are not a new phenomenon, they have been increasing in recent years (1, 2), prompting international concern about long-term supply of key medicines.

A technical consultation was hosted by WHO in December 2015 to discuss the bottlenecks and reasons for shortages, consider existing solutions and identify approaches that could be effective at the global scale (3). The discussions built on the findings and recommendations of an earlier summit meeting convened by International Pharmaceutical Federation (FIP) in 2013 (4).

Types of medicines affected

Available data indicate that products in short supply include many commonly used medicines such as antibiotics, cancer medicines, cardiovascular medicines and anaesthetics. Many of them are off-patent products and are difficult to formulate or have a tightly defined shelf life. This combines with characteristics at the levels of manufacturers, buyers and supply chains as described below.

As a first step in defining a global list of essential medicines at risk of shortages a preliminary analysis was presented at the meeting, comparing the WHO Essential Medicines List (EML) with four
current public databases of medicines in short supply. Adrenaline (epinephrine) and atropine sulfate were listed in all the databases reviewed, and many antibiotics – especially the cephalosporins – were listed in three out of the four databases. A well-studied example of an affected antibiotic is benzathine penicillin, which has been in chronic short supply for several years with global implications (5). Another example is insulin, which can be accessed reliably by only half of the 100 million people around the world who need it (6). Children’s medicines are also often affected by shortages, representing a separate and important issue.

Factors contributing to shortages
A range of causes and contributing factors combine to create situations where the demand for a medicine is not met by adequate supply.

Demand side
Unexpected demand changes or fluctuations can lead to medicines shortages, and the risk increases with the use of just-in-time inventory control where facilities sometime hold no or insufficient buffer stock. Uncertain availability can in turn lead to “hoarding” and to informal exchange of stock through the grey market, posing risks for drug quality.

With increasing international funding for treatment of priority diseases there has been an increased demand for certain medicines in low- and middle-income countries that have not historically been large buyers in the global markets. Significant demand changes can occur in this global marketplace, for example due to changing treatment guidelines. In case of a shortage, local attempts at solutions sometimes merely transfer a shortage from one country to another.

A host of factors challenge the successful procurement of medicines from global markets. Commonly reported problems include fragmented demand, rigid rules on tenders, rigid shelf life requirements, overly customized specifications and payment issues. All this can lead to manufacturers refusing to participate in tenders, or holding orders until they combine to full batch quantities to be able to supply from fresh production.

At the supply chain level, unreliable data from peripheral facilities continue to be a major problem in most low- and middle income countries, hindering coordinated stock management and effective forecasting.

Box 1: Medicines shortages: a widespread and persistent problem
- In the U.S., new drug shortages rose from 70 in 2006 to a high of 267 in 2011. The total number of new and ongoing shortages crossed the 450 mark in 2012 (1). In an example cited by FIP, shortages cost U.S. hospitals US$ 416 million, i.e. US$ 200 million to purchase more expensive alternatives and US$216 million in labour costs.
- In a large European survey, 21% of hospital pharmacists reported experiencing a shortage of medicines every day, a further 45% every week. One in five pharmacists felt that they could not manage the shortage all or most of the time, suggesting that medicines shortages cause patients to suffer disruption to their treatment. (2)
- Fewer data are available from low- and middle-income countries. However, the experiences reported at the meeting by national and international actors suggest that there are significant challenges in ensuring access to needed medicines.
Payment systems can cause problems in both high-income and low-income countries. Limited health budgets are creating downward pressure on prices, threatening manufacturers’ ability to maintain quality manufacturing. However, sudden changes in payment structures or perverse incentives to use expensive products seem to cause as much trouble as not having sufficient funds.

**Supply side**
For a viable market model, a supplier base of at least three different manufacturers is generally considered desirable. For some needed products, particularly those which are less attractive from a marketing perspective, the manufacturing base is very limited. Mergers and acquisitions have further reduced the number of manufacturers that produce certain finished products. For instance, in the U.S., the majority of the injectable generic products is supplied by only seven major manufacturers (4).

Medicines shortages have been increasingly related to quality and raw material problems at the manufacturing level. In the globalized pharmaceutical markets there is an increased competition for active pharmaceutical ingredients (API). There has been a move towards API suppliers from emerging economies, such as India and China, which have come to experience tensions in catering for local and international demands and quality standards. Yet these sources cover a significant part of global API needs and are not easy to replace at short notice.

Maintaining quality systems for finished pharmaceutical products in line with current, international standards has become a complex and expensive endeavour. Moreover, long timelines to regulatory approval and diverse or frequently changing regulatory requirements make market entry in many target countries costly and unpredictable. These challenges contribute to quality-assured finished products of certain essential medicines being scarce on the global pharmaceutical market.

**Meeting recommendations**

*Risk-based public health approach*
Noting that shortages of medicines directly impact the health of patients, the meeting participants emphasized that a patient-centred approach to managing medicines shortages is required. Risk management principles should be used to identify and prioritize measures to ensure the continued supply of the medicines that are most needed in public health systems.

*Effective stakeholder discussion*
Coordination, communication and transparency should be fundamental principles in all actions between stakeholders at the national, regional and global level. Civil society and professional associations should continue to play a role in preventing and managing global stock outs. With their position in communities and other forums, they frequently have access to information that would be useful in detecting, or responding to, medicines shortages.

*Procurement*
Understanding global and national demand, especially for vulnerable products, was recognized as important. The experience of market shaping by global organizations could be leveraged. It should be noted that existing strategies have often been developed for medicines with single indications managed under specialized treatment programmes – such
as vaccines or antiretrovirals – and would likely fail for many of the medicines that have indications across several categories of general medicine.

Tender and procurement practices should be critically reviewed to identify possible causes of shortages. While there may not be a single perfect solution, it was recognized as necessary to consider the nature of each product, the available alternatives on the market as well as market demand in establishing tender conditions. Approaches that have improved the availability of certain medicines in pooled procurement mechanisms could be considered, such as advanced purchase commitments for priority drugs, engagement of manufacturers, credit facilities that promote consistency and predictability of cash flows, and consolidation of product specifications.

Supply chain management
Participants agreed that the importance of promoting efficient and effective management throughout the supply chain cannot be overemphasized.

IT systems that facilitate both upstream and downstream collection of information need additional support. Rapidly advancing the use of standardized bar coding – for example using GS1 as a common standard – was acknowledged as important and feasible.

Ethical medicines use
Ethical approach to management of shortages were discussed using examples from specialist areas of medicine, such as paediatric oncology, and national experiences for example in Canada. Suggested principles include evidence-based clinical decisions, fair access to medicines across different populations, including clinical trial patients, and across phases of treatment. It was also proposed that criteria should be defined to prioritize the use of medicines in short supply, noting that this may be controversial. Ideally, agreement on a management approaches should be reached before shortages occur.

Pricing
A fair medicines price must be viable for the supplier and affordable for the buyer.

Exceedingly high prices are making some patented medicines unaffordable for health systems, and measures to ensure affordability have been much discussed for example for antiretrovirals a decade ago, and more recently for cancer treatments and new medicines to treat tuberculosis and hepatitis C. Meeting participants felt that negotiation with the patent holder to reach a mutually acceptable agreement should be the first approach. If this fails, the flexibilities of the TRIPS agreement such as compulsory licencing can be used; however this has significant costs and implications and should be carefully considered.

At the other end of the spectrum, the low prices of certain off-patent medicines are contributing to medicines shortages. For example, methotrexate is crucial to the treatment of many oncological and immunological conditions, yet it has been reported as in short supply repeatedly. Would an agreed global minimum price help keep it on the market? How would such a price be set? Meeting participants agreed that more transparency about the cost of production and the basis for pricing would be helpful to enable a constructive dialogue between manufacturers and procurement groups.
Regulation
Drug regulators themselves have limited scope for action, since while they can keep a drug off the market, they cannot require a company to make a product. Approaches to prevent and mitigate supply interruptions, such as mandatory notification by manufacturers of current or impending shortages, and expedited inspections and reviews to incentivize manufacturing of good quality needed products, have been adopted for example by the U.S. FDA (7).

The value of good practices in responding to shortages, and of understanding the interaction and impact of regulatory decisions on availability of medicines, was recognized. Regulatory best practices should be collected, where possible harmonized, and provided as guidance to others.

National reporting systems
Notification systems of medicines shortages exist in most high-income countries but are not yet required in many low- and middle-income countries (LMIC). However, existing databases have different definitions and approaches. For example, a “shortage” may be reported when health facilities are unable to pay for medicines, which does not mean that the product is unavailable on the market. In some databases the reason of shortage is given as “unknown” for almost half of the reported stock-outs.

It was agreed that it would be essential to harmonize definitions of “stock outs” and “shortages”, noting that work has commenced on this in some groups, and to establish standards for reporting that can be used for databases generally. Harmonization of reporting systems according to best practice would facilitate collaboration between regulators and would support countries without an existing mechanism in establishing one.

Global notification system
A global reporting mechanism could provide valuable insight into the development of the global medicines market. Such a system could monitor a list of medicines yet to be prioritized based on product and market characteristics. Data contributed to a global reporting mechanism would need to be from verified sources and must be validated. The value of having public access to databases as well as public reporting was clearly recognized.

Way forward
The following priorities for WHO were identified based on the meeting outcomes:
1. Develop a consolidated list of medicines that are in short supply and are critical for use in medicine (from the WHO essential medicines list) or are at risk of short supply.
2. Develop an approach to market shaping for these medicines in collaboration with global partners.
3. Facilitate harmonization of definitions used in relation to shortages.
4. Consider development of a global shortage notification system, resources permitting.
5. Facilitate development of global best practices for regulatory authorities in relation to notification and management of shortages, including data standards, database management and regulatory/legislative strategies to minimize impact of shortages.
6. Work with partners such as global industry representatives and professional associations to develop good practice standards in managing shortages.
7. Work with global partners to develop consolidated volume and consumption data for ‘vulnerable’ medicines.
8. Work with partners to develop appropriate pricing strategies to ensure supply of ‘vulnerable’ medicines.
9. Continue to support countries, with global partners, to improve supply chain management, including up to date guidance and policies.

The issue of drug shortages was brought to the attention of the WHO Executive Board in January 2016 (8) and will be discussed as a specific topic for the first time at the World Health Assembly in May 2016.

Conclusions
Shortages of key medicines will likely continue to be a problem. Meeting participants recognized that shortages of medicines and technologies are of concern to all countries, and that a coordinated, end-to-end approach across the health system is needed to mitigate their impact on public health. Global institutional leadership will be required to move forward on priority issues for improving access to needed medicines in health systems.

References
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Concept paper for discussion

A stepwise approach for pharmaceutical companies in developing countries to attain WHO GMP standards

This concept paper aims to provide a risk-based, phased approach for development of a country-specific, achievable roadmap towards WHO GMP for the manufacture of finished pharmaceutical products in low- and middle-income countries. The concept paper is based on the experience of the United Nations Industrial Development Organization (UNIDO) in developing and implementing national level GMP roadmaps. It describes the concept, the tools that have been developed and the process utilised for implementation. It is proposed for discussion on how policy makers and regulators can mitigate risk to public health during transition of an industry to GMP compliance based on a risk-based, phased roadmap.

Comments and suggestions on this paper are invited to facilitate further discussion. They should be sent to druginfo@who.int.

Introduction

Background
Adherence to Good Manufacturing Practices (GMP) is essential for consistent quality assurance of medicinal products and is important for ensuring their consistent safety and efficacy. However, due to the lack of financial, technical and human resource capacities, pharmaceutical manufacturers in developing countries are often overwhelmed by the vast array of GMP requirements and therefore fail to operate in line with such internationally acceptable standards. The situation is fuelled by the fact that regulatory authorities in many developing countries cannot meet the demands associated with internationally acceptable GMP standards. Of the more than 190 WHO Member States only “about 20% are known to have well developed drug regulation” whereas “30% either have no drug regulation in place or a very limited capacity that hardly functions” (1). As a result, pharmaceutical companies located in developing countries frequently feature operating environments and procedures that fall below standards that should ultimately be acceptable. Due to the lack of unified quality requirements, individual companies trying to improve their manufacturing standards are struggling to remain competitive in the low-priced market while many manufacturers are discouraged from making the necessary investments that are required to upgrade. According to WHO low- and middle-income countries bear the greatest burden of substandard products (2), whereby the rate of substandard

This document has been prepared by Kay Weyer, Ph.D., UNIDO Senior Pharmaceutical Manufacturing Expert (Consultant). It is largely based on the document listed as Reference 10 on page 196.

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products can even exceed 60% in particular countries for certain life-saving drugs such as anti-malarials (3). The use of substandard medicines can lead to harmful and even lethal consequences including therapeutic failure, drug resistance or toxicity.

Thus, there clearly exists an urgent need for improvement of existing manufacturing standards. However, there are significant challenges to raising standards. A central requirement to address the multitude of issues is the establishment of a stepwise technical pathway towards GMP compliance based on an assessment of the current situation within a country.

**Purpose**

This concept paper explains UNIDO’s approach to developing a country-specific, achievable roadmap towards internationally acceptable GMP standards, such as those issued by the World Health Organization (WHO). The paper points out the need for a risk-based, phased roadmap towards WHO GMP compliance and explains required steps and tools for its development.

The purpose of this document is to provide the technical aspects of developing a stepwise, phased, and risk-based approach for pharmaceutical manufacturers to reach full WHO GMP compliance. This roadmap shall set the path for the industry in individual countries to progress within a specified period of time to compliance with the internationally acceptable GMP standards defined by WHO.

The document also highlights the various benefits that such a GMP roadmap approach has for the pharmaceutical sector in developing countries. Finally, this paper provides an example of the successful application of the roadmap concept in a developing country as evidenced by the implementation of the Kenya GMP Roadmap (6).

This document should be read in conjunction with the respective WHO GMP guidelines mentioned in Footnote 1.

**Scope**

This document focuses on WHO GMP requirements for the manufacture of medicines in their finished dosage forms.

Although the concept was initially developed for the manufacture of non-sterile dosage forms containing small molecular entities, the strategic approach presented in this paper can be applied to various GMP environments as long it is ensured that internationally recognized GMP guidelines are utilized as reference standard and that risks resulting from existing manufacturing practices are adequately mitigated during the progress of companies from existing practices to full compliance with GMP.

**GMP roadmap concept**

**Need for a risk-based, phased approach towards WHO GMP**

Observations from GMP inspections performed by WHO at manufacturers of medicinal products in developing countries revealed a high number of deviations from WHO GMP, including some critical deficiencies posing a potential risk of harm to patients (7). GMP compliance assessments conducted recently by UNIDO as part of the GMP roadmap work resulted in the observation of similar deficiencies, underlining the urgent need for improvement of existing manufacturing standards. For the majority of pharmaceutical manufacturers in developing countries the gap between WHO GMP requirements and current manufacturing practices is
substantial. Therefore, the transition from current manufacturing practices to full compliance with WHO GMP standards is a time-consuming process which cannot be achieved overnight. In order for the upgrading approach to be realistic and achievable, a stepwise, phased pathway with clearly defined milestones and targets at the end of each phase should be developed, guiding the pharmaceutical sector from the status quo to the targeted WHO GMP compliance.

While developing such an approach, it is essential to identify those areas of WHO GMP where companies are least compliant. These areas pose the biggest threat to the quality, safety and efficacy of the medicinal products manufactured and therefore have to be addressed with priority in order to avoid exposing patients to preventable risks.

In summary, this highlights that to ensure an achievable and hence realistic pathway towards full WHO GMP compliance the roadmap approach has to be

- risk-based, focusing first on those areas of WHO GMP with which least compliance exists and which are hence posing the highest risk to the quality, safety and efficacy of medicines manufactured; and
- structured in phases allowing a stepwise transition to full WHO GMP compliance with clearly defined targets at the end of each phase.

**Steps for a risk-based, phased approach towards WHO GMP compliance in a specific country**

**Step 1: Baseline assessment of existing manufacturing practices**
The baseline assessment is the starting point for the development process leading to a GMP roadmap. During the baseline assessment field studies are performed on a sample of pharmaceutical manufacturers which have not yet achieved full compliance with WHO GMP. Thereby it has to be ensured that the sample of pharmaceutical manufacturers selected for the baseline assessment is representative of the various levels of compliance with WHO GMP within a country.

WHO GMP is a highly suitable GMP reference standard as it is based on unified principles and practices agreed by the world’s leading regulatory agencies and hence receives wide international acceptance. Besides, many pharmaceutical manufacturers in developing countries strive to achieve compliance with WHO GMP as part of the requirements for having their products prequalified by WHO.

It is essential that this baseline assessment is well prepared and conducted thoroughly, as its results provide the basis for the specific design of the GMP roadmap. Therefore, unified tools have to be developed and applied equally to all pharmaceutical manufacturers participating in the baseline assessment in order to ensure transparency and consistency of obtained results. These tools include 1) the definition of key elements and focus areas during assessments; 2) preparation of an assessment schedule to be applied to all companies; and 3) the definition of rating of observations.

WHO GMP can be divided into 17 key areas which are called “key quality elements”, listed below.

1. Pharmaceutical Quality System
2. Utilities impacting Good Manufacturing Practices (GMP)
3. Sanitation and hygiene
4. Qualification and validation
5. Complaints
6. Product recalls
7. Contract production, analysis and other activities
8. Self-inspection, quality audits and suppliers’ audits and approval
9. Personnel
10. Training  
11. Personal hygiene  
12. Premises  
13. Equipment  
14. Materials  
15. Documentation  
16. Good practices in production  
17. Good practices in quality control  

For each of these key quality elements the assessment focus has to be defined. Based on the defined key quality elements and focus areas, an assessment schedule is prepared which is uniformly applied to all companies. In order to allow for a thorough assessment while at the same time avoiding too lengthy a time period for the field study, it is recommended that the assessment of each company takes two full days. Deficiencies of individual companies observed during the assessment are rated using a standard rating scheme of “critical”, “major”, “other”, as outlined for example in the compilation of EU “Community Procedures on Inspections and Exchange of Information” (8).

Step 2: Evaluation of assessment results and identification of common main technical challenges  
In order to evaluate the level of compliance with WHO GMP and to identify the main technical challenges across the range of pharmaceutical companies within individual countries, two tools have been developed:
1. Identification of key quality elements affected by highest and lowest compliance with WHO GMP; and  
2. Risk categorization of companies based on their compliance with WHO GMP.

Tool 1: Identification of key quality elements affected by highest and lowest compliance with WHO GMP  
Using the plain ratings of individual observations made during each company assessment would not be suitable to identify common main challenges across the pharmaceutical sector in a given country. Rather, a tool is required to compare individual companies in terms of their compliance with WHO GMP and to identify those key quality elements where highest and lowest compliance rates are observed. Therefore, a rating scheme has been developed that enables aggregation of individual observations related to a specific key quality element so as to reflect its composite compliance with WHO GMP requirements. The rating scheme comprises the following three levels:

- Compliance of a key quality element with WHO GMP is rated “acceptable” if no or only “other” (i.e. “minor”) deficiencies have been observed in areas related to this specific key quality element.
- Compliance of a key quality element with WHO GMP is rated “requires improvement” (short: “improve”) if only few “major” deficiencies (n ≤ 5) were observed in areas related to this specific key quality element.
- Compliance of a key quality element with WHO GMP is rated “inadequate” if at least one “critical” and/or a considerable number (n > 5) of “major” deficiencies are observed in the respective area or if the entire key quality element is not available at a company.

This rating key makes it possible to compare company performances and to identify those key quality elements for which highest and lowest compliance has been observed. In this way the main technical challenges for compliance can be identified. The rating key is a useful tool to evaluate particular weaknesses in compliance of pharmaceutical manufacturers within a country.

The described evaluation tool can also be used for trending of GMP compliance of companies and for monitoring their development towards full WHO GMP compliance throughout the implementation of the roadmap.
**Tool 2: Risk categorization of companies based on their compliance with WHO GMP**

GMP compliance can be understood as the result of compliant structural and compliant organizational measures. In this paper the term “site” applies to the physical entity of mainly premises, utilities and equipment used for pharmaceutical manufacturing. The term “quality management system (QMS)” is applied for all documentation systems and procedures used by a company to ensure GMP compliance. The interconnection between site, QMS and GMP is illustrated in Figure 1.

The risk classification uses a matrix to categorize companies based on the two risk-indicating factors for GMP compliance: 1) Compliance of site with WHO GMP standards; and 2) Compliance of quality management system with WHO GMP standards.

A score of “1”, “2” or “3” is assigned to both the site and the quality management system to describe their respective degree of compliance with WHO GMP. A score of “3” represents high compliance-related risk whereas a score of “1” indicates low compliance-related risk.

A matrix is used for combining these two scores in order to generate an estimate of the overall compliance-related risk associated with a pharmaceutical manufacturer (Table 1). The resulting risk ratings are “A”, “B” and “C”, with a rating of “C” representing a high-risk company and a rating of “A” indicating a low risk company.

In order to increase the transparency and objectivity of the scores given for the compliance of site and QMS with WHO GMP, indicator criteria have been defined which are presented in Annex 1.

This risk categorization is a suitable tool for benchmarking GMP compliance of companies and can also be used in conjunction with “Tool 1” to monitor the companies’ progress in the upgrading process towards full WHO GMP compliance.

Additionally, the tools presented above can be utilized by individual pharmaceutical manufacturers in the context of a gap analysis and in order to prioritize and streamline corrective and preventive actions (CAPA).

**Step 3: Design of a GMP roadmap based on evaluation results**

Based on the evaluation outcomes a risk-based, phased GMP roadmap can be designed. Tool 1 identifies the key quality elements for which the most severe deficiencies versus WHO GMP exist and hence identifies the main technical challenges for the sector within the country which need to be addressed with highest priority. Tool 2 allows one to determine whether the main reason for
low compliance with WHO GMP is caused by site- or QMS-related aspects of GMP, which helps to streamline the upgrading approach. Furthermore, this tool allows one to characterize the currently predominating level of compliance-related risk associated with pharmaceutical manufacturers within a country, and provides guidance in determining the number of phases needed to achieve full compliance with WHO GMP. If the predominantly existing compliance-related risk of the pharmaceutical companies in a country is rated as class “C” (i.e. predominance of high risk companies with inadequate manufacturing standards and procedures impairing production safety) at least 2 main phases will be needed to gradually improve from the existing level to full WHO GMP compliance: Phase I from level “C” to “B” will primarily focus on reducing the risk to production safety, Phase II from level “B” to “A” will aim to achieve full compliance with WHO GMP. In this context, it is well acknowledged that depending on the outcome of the evaluation it might be advisable to further divide the main phases into sub-phases. The content of those (sub-)phases will be primarily defined by the outcome of the compliance assessment of the key quality elements, with the first phase focusing particularly on those elements that show the most severe deviations from WHO GMP. Whether the first phase will put emphasis on site- or QMS-related GMP aspects will depend on the outcome of the company risk assessment to the extent that a distinct trend of compliance-related risk distribution between the two aspects is revealed.

As the individual phases of the GMP roadmap are defined according to the severity of deficiencies versus WHO GMP and the compliance-related risk observed at pharmaceutical manufacturers, the evaluation results are instrumental in realizing a stepwise, risk-based approach towards achievement of full WHO GMP compliance.

A: Existing approach towards pharmaceutical manufacturing in general in line with WHO GMP requirements → low-risk company
B: Existing approach towards pharmaceutical manufacturing not in line with WHO GMP but reduced risk with regard to production safety → medium-risk company
C: Existing approach towards pharmaceutical manufacturing not in line with WHO GMP and high risk with regard to production safety → high-risk company

### Table 1: Risk matrix for the categorization of companies based on their GMP compliance

<table>
<thead>
<tr>
<th>Quality Management System (QMS)</th>
<th>3 – No QMS in place</th>
<th>2 – Requirements are implemented sporadically only; a systematic approach to GMP is not in place</th>
<th>1 – A systematic approach in line with WHO GMP in place and implemented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – Site is in general compliant with WHO GMP</td>
<td>C</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>2 – Site shows significant deficiencies versus WHO GMP, but production safety is not impaired</td>
<td>C</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>3 – Site unsuitable for pharmaceutical manufacturing → production safety impaired</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

A: Existing approach towards pharmaceutical manufacturing in general in line with WHO GMP requirements → low-risk company
B: Existing approach towards pharmaceutical manufacturing not in line with WHO GMP but reduced risk with regard to production safety → medium-risk company
C: Existing approach towards pharmaceutical manufacturing not in line with WHO GMP and high risk with regard to production safety → high-risk company
Benefits of a risk-based, phased roadmap towards WHO GMP

A risk-based, phased approach towards WHO GMP compliance has many benefits for the pharmaceutical sector of developing countries, including the following.

- The development of a risk-based, phased roadmap results in an achievable and scientifically sound pathway towards internationally acceptable GMP standards, which will eventually lead to a significant reduction of substandard medicines.
- A step-wise transition of pharmaceutical manufacturing practices towards a unified, internationally acceptable quality standard following clearly defined requirements, activities and milestones ensures the presence of a level playing field throughout the phases of the roadmap.
- The risk-based, phased roadmap ensures that all stakeholders have the same understanding of GMP throughout each of the transition phases,
  - demystifying requirements of WHO GMP and hence leading to an increased willingness to implement WHO GMP by the industry, and
  - increasing transparency during licensing procedures and regulatory GMP inspections and hence strengthening regulatory authorities.

A well-defined risk-based, phased roadmap will enable:

- already existing companies to perform a gap analysis between their current GMP compliance and WHO GMP requirements and to follow a stepwise approach towards WHO GMP compliance;
- new start-up companies to assure that all necessary elements and systems are taken into consideration and are in place before the actual launch of the company; and
- the regulatory authority to review licensing criteria for new and existing facilities, allowing existing companies to improve gradually until they are in line with WHO GMP requirements and ensuring that new companies comply with WHO GMP before their licensing.

Outlook on aligning the approach with other stakeholders’ activities

The risk-based, phased roadmap towards WHO GMP has to be anchored as a key component in a holistic approach for the development of the pharmaceutical manufacturing industry. In addition to a GMP roadmap many other components essential for the industrial development of the pharmaceutical sector in developing countries have to be taken into consideration. Those components, which include strengthening of the regulatory functions, access to affordable finance, development of incentive schemes, development of necessary human resources and securing distribution chains have to be addressed to enable sustainable high quality local production to be achieved through the GMP roadmap approach.

While the roadmap approach presented by UNIDO in this concept paper focuses on improving the quality of pharmaceutical manufacturing, other stakeholders, especially the Essential Medicines Department of WHO, are working on a risk assessment regarding the suitability of products for manufacture in companies according to their respective levels of compliance to WHO GMP. Both organizations have acknowledged the complementarities of the respective methodologies and have indicated willingness to incorporate them into a joint approach correlating the phases of the roadmap and the risk classification of pharmaceutical manufacturers with product manufacturing requirements.
A practical example of successful development of a risk-based, phased roadmap to WHO GMP compliance

The approach outlined above has been used to develop GMP roadmaps for Kenya and Ghana delineating the pathway from existing GMP compliance to full WHO GMP compliance. Country-specific roadmaps were devised taking into consideration the main technical challenges faced by manufacturers of medicinal products.

The development of the Kenya GMP Roadmap (6) is described here as a practical example for the successful development of a risk-based, phased GMP roadmap using the aforementioned approach.

The baseline assessment of existing manufacturing practices was performed at seven pharmaceutical companies that, while all falling short of full WHO GMP compliance, represented the different levels of manufacturers in the country. The scope of the baseline assessment was limited to the manufacture of small molecule, non-sterile medicinal products. The results shown below are anonymized and the sequence of the companies assessed is randomized, not allowing participants to be traced.

Using evaluation tool 1 the compliance of participating companies with key quality elements of WHO GMP was assessed. The results of this assessment, as shown in Figure 2, indicate that the companies’ compliance with WHO GMP was not rated acceptable for the majority of key quality elements.

Figure 2 also shows that seven key quality elements were associated with the lowest possible compliance rating (i.e. inadequate) in more than half of the participating companies. The elements listed below should be addressed with priority as they pose

![Figure 2: Compliance of participating companies with key quality elements of GMP](image)

* Key quality elements written in red indicate those for which the highest number of companies showed least compliance.

** As the assessment had been performed before TRS 986, Annex 2 (5) became official, terms used for the key quality elements were based on TRS 961, Annex 3 (9), e.g. the term “Quality assurance” was used instead of “Pharmaceutical quality system”.
the most severe risk to quality, safety and efficacy of the manufactured products:
- Quality assurance
- Utilities impacting Good Manufacturing Practices (GMP)
- Sanitation and hygiene
- Qualification and validation
- Premises
- Material handling
- Good practices in quality control

Evaluation tool 2 was used to categorize participating companies regarding their compliance with WHO GMP based on two risk-indicating factors, namely:
- Compliance of site with WHO GMP standards
- Compliance of quality management systems with WHO GMP standards

The results are displayed in Table 2.

<table>
<thead>
<tr>
<th>Company name</th>
<th>Risk score Site</th>
<th>Risk score QMS</th>
<th>Overall GMP rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company 1</td>
<td>2</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>Company 2</td>
<td>2</td>
<td>2</td>
<td>B</td>
</tr>
<tr>
<td>Company 3</td>
<td>3</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Company 4</td>
<td>3</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Company 5</td>
<td>3</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Company 6</td>
<td>3</td>
<td>2</td>
<td>C</td>
</tr>
<tr>
<td>Company 7</td>
<td>3</td>
<td>3</td>
<td>C</td>
</tr>
</tbody>
</table>

The risk assessment shows that out of the seven companies assessed only two achieved an overall GMP rating of “B” (medium risk company) whereas the remaining companies received an overall GMP rating of “C” (high risk company). The risk scores for compliance of the QMS with WHO GMP requirements ranged from “1” to “3”, the risk scores for compliance of the site with WHO GMP requirements ranged from “2” to “3”. This result underlines that the selection of companies was suitable for the assessment, as the selection criteria were to include companies representing different levels of GMP compliance (risk scores between “1” and “3”) while having not yet achieved full compliance with WHO GMP (no company with an overall GMP rating of “A”).

The risk assessment reveals that in general the scores for the site were higher than those related to the QMS. The usually higher risk associated with site was for almost all companies the main cause for downgrading the overall GMP compliance rating. This clearly indicates that particular guidance is needed regarding site-related GMP aspects and design requirements.

The following conclusions can be drawn from the assessment performed at pharmaceutical companies in Kenya and needed to be reflected in the design of the roadmap to WHO GMP compliance:
- Site-related GMP aspects need to be prioritized for improvement.
- Immediate measures are also required to reduce product-related risks caused by inadequacies of the QMS, with a special focus on those key quality elements with the lowest observed compliance ratings.

Taking into account the evaluation results, a risk-based, two-phased approach has been designed for the Kenya GMP Roadmap as shown in Figure 3.

Phase I focuses on the mitigation of risks impairing production safety by establishment of WHO GMP compliant sites and improvement of those QMS elements for which the majority of companies showed the most severe deficiencies versus WHO GMP (“QMS 1”). Using the results of the risk assessment, the majority of companies initially rated as “C” should reach a “B” rating at the end of Phase I as their sites (being a main contributory factor for their low GMP compliance rating) should then be in line with
WHO GMP requirements. Besides, those key quality elements for which the majority of companies showed least compliance will be in line with WHO GMP requirements at the end of Phase I, enabling companies to have at least a sporadic implementation of QMS in place.

During Phase II the main focus will be on establishing a comprehensive, WHO GMP compliant quality management system ("QMS 2") so that ultimately both structural ("site") and organizational ("QMS") measures for GMP compliance will be in line with WHO GMP. As the definition of the individual phases of the GMP roadmap is based on both the severity of deficiencies versus WHO GMP and the compliance-related risk observed at Kenyan pharmaceutical manufacturers, a stepwise, risk-based approach has been realized for the Kenyan roadmap towards achievement of full WHO GMP compliance. This technical roadmap provides for each of its phases a detailed breakdown of required actions and milestones for improvement of site-related and QMS-related GMP aspects. The structure of the Kenya GMP Roadmap is provided in Annex 2.

The roadmap has been complemented with an implementation plan embracing all facets required for successful implementation of the Kenyan roadmap towards compliance with WHO GMP requirements including definition of near- and mid-term requirements. The roadmap and implementation plan were agreed and endorsed by key stakeholders including representatives from industry and government (both policy-makers and regulators) during meetings in 2013 and 2014 and are part of the implementation of the Kenyan Pharmaceutical Sector Development Strategy.

The targeted timeline for implementation of the Kenya GMP Roadmap, as agreed amongst all stakeholders, is five years, whereby the first phase is targeted to take no longer than three years; and the second phase is targeted to be completed within two

**Figure 3:** Risk-based, phased approach of the Kenyan roadmap towards achievement of full WHO GMP compliance

<table>
<thead>
<tr>
<th>Overall GMP compliance rating</th>
<th>Phase focus and targeted outcomes</th>
<th>Phase number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Site and Quality Management Systems in line with WHO GMP requirements</td>
<td>Improvement and implementation of those QMS with identified lower risk (QMS 2)</td>
<td>— Phase II</td>
</tr>
<tr>
<td><strong>B</strong> Site generally in line with WHO GMP requirements / QMS 1 in line with WHO GMP requirements</td>
<td>Improvement and implementation of those QMS for which majority of companies showed least compliance (QMS 1)</td>
<td>— Phase I</td>
</tr>
<tr>
<td><strong>C</strong> Site and Quality Management Systems not in line with WHO GMP requirements</td>
<td>Construction / modification of sites as per WHO GMP requirements</td>
<td>—</td>
</tr>
</tbody>
</table>
years. The time allocated to Phase I is longer due to the need for modification of existing sites or construction of new sites during this phase.

In line with the implementation plan for the roadmap all Kenyan manufacturers of finished pharmaceutical products were assessed by internationally experienced GMP inspectors in conjunction with inspectors from the Pharmacy and Poisons Board in 2015. The outcome of the gap analysis project confirmed observations, conclusions and prioritizations made based on the baseline assessment for the development of the GMP Roadmap and hence verified the adequacy of the approach and the aforementioned tools used for the development of the GMP roadmap.

Conclusion
This document summarizes a methodology to develop a pathway for pharmaceutical manufacturers in developing countries to move towards WHO GMP standards. In order to be manageable and scientifically sound, the GMP roadmap should be risk-based and structured into phases. The concept has been successfully applied in Kenya and Ghana where country-specific GMP roadmaps have been developed in consultation with key domestic stakeholders including the pharmaceutical industry, regulators and relevant governmental departments. Assessments of all Kenyan manufacturers of finished pharmaceutical products by internationally experienced GMP inspectors in conjunction with inspectors from the Pharmacy and Poisons Board confirmed the observations, conclusions and prioritizations made based on the baseline assessment for the development of the Kenya GMP Roadmap and hence verified adequacy of the approach and the tools used for development of the GMP roadmap.

References
7 Thrussell I. Examples of critical and major observations from GMP inspections of Manufacturing, QC and Contract Research Organisations. Presented at the UNICEF Pharmaceutical Supplier Meeting 2012 on 26 September 2012.
The Kenyan roadmap towards achievement of full WHO GMP compliance

Source: (6)

Annex 1: Indicator rating system

Indicator criteria have been defined in order to increase transparency when rating the compliance risks associated with “Site” and “Quality Management System” (“QMS”) of the companies assessed. A score of “3” represents a high compliance risk, whereas a score of “1” represents a low compliance risk.

Indicators for score criteria for site

<table>
<thead>
<tr>
<th>Prerequisite</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premises</td>
<td>Premises are designed to be suitable for pharmaceutical manufacturing</td>
<td>Premises show significant deficiencies from WHO GMP but do not impair production safety</td>
<td>Premises are unsuitable for pharmaceutical manufacturing → Production safety impaired</td>
</tr>
<tr>
<td>Utility</td>
<td>Utilities which have direct product contact (e.g. water, air handling, compressed dried air) are in place as required, suitable and effective/ functioning</td>
<td>Utilities which have direct product contact (e.g. water, air handling, compressed dried air) are in place as required but not fully compliant with WHO GMP</td>
<td>Utilities which have direct product contact (e.g. water, air handling, compressed dried air) are not available although required, or available utilities are unsuitable</td>
</tr>
<tr>
<td>Equipment</td>
<td>Equipment for all manufacturing steps and quality controls are suitable to perform the operation and functioning</td>
<td>Equipment for at least critical manufacturing steps and quality controls are in place and suitable to perform the operation and functioning</td>
<td>Equipment for critical manufacturing steps and quality controls are not available or not functioning</td>
</tr>
</tbody>
</table>

When assigning the overall site rating, the rating (1, 2 or 3) which best reflects the various individual ratings that were assigned to the site attributes should be chosen.

Indicators for score criteria for QMS

<table>
<thead>
<tr>
<th>Prerequisite</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMP documentation and procedures</td>
<td>A systematic holistic approach towards GMP documentation is in place; procedures performed are adequate and based on a documented system</td>
<td>No systematic approach towards a documentation system is in place; sporadic implementation of GMP requirements; procedures performed are not always based on a documented system</td>
<td>No GMP documentation is in place; procedures are totally inadequate</td>
</tr>
<tr>
<td>Calibration/ qualification/ validation</td>
<td>A systematic approach based on master documents, schedules, protocols and reports is in place</td>
<td>Checks for performance of critical equipment, instruments and methods done but not to an extent required and/or not based on a systematic approach</td>
<td>No calibration, qualification, validation are performed</td>
</tr>
<tr>
<td>Preventive maintenance</td>
<td>Comprehensive preventive maintenance procedures based on a systematic approach are in place.</td>
<td>Preventive maintenance for critical systems is performed but no systematic approach including schedules, protocols, reports/logs is in place</td>
<td>No preventive maintenance is performed.</td>
</tr>
<tr>
<td>Sanitation</td>
<td>Cleaning is adequate; a systematic approach to cleaning consisting of validation, cleaning schedules, logs is in place</td>
<td>No signs of inadequate cleaning are observed, but no systematic approach to cleaning including cleaning validation, schedules, logs is in place</td>
<td>Evidence of widespread accumulation of residues/ extraneous matter exists; evidence of gross infestation is observed</td>
</tr>
<tr>
<td>Material handling</td>
<td>Documented procedures for all types of material handling are in place in line with pharmacopoeia/ international guidelines</td>
<td>Testing of materials/products is performed but not to the extent required by pharmacopoeia and international guidelines. Procedures for receipt, sampling, storage, manufacturing and distribution are defined but documentation is not in place for all operations</td>
<td>No testing of materials/products is performed. Procedures for receipt, sampling, storage, manufacturing and distribution are inadequate; no GMP documentation is in place</td>
</tr>
</tbody>
</table>
Indicators for score criteria for QMS (continued)

<table>
<thead>
<tr>
<th>Prerequisite</th>
<th>Rating</th>
<th>Prerequisite</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel/training</td>
<td>1</td>
<td>Personnel has the right qualification, experience and knowledge to perform duties assigned, training program is in place</td>
<td>Personnel has the right qualification and knowledge to perform duties assigned, but no training program is in place</td>
</tr>
</tbody>
</table>

When assigning the overall QMS rating, the rating (1, 2 or 3) which best reflects the various individual ratings that were assigned to the QMS attributes should be chosen.

Annex 2: Exemplary structure of the Kenya GMP Roadmap

Start: Site and quality management systems not in compliance with WHO GMP requirements

Section 1.1: Phase I, Site

<table>
<thead>
<tr>
<th>Phase/Ref. No.</th>
<th>Key quality element</th>
<th>Actions for implementation</th>
<th>Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1</td>
<td>Premises</td>
<td>Define scope of premises by taking into account:</td>
<td>Scope of the premises defined</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Environment in which the premises are built</td>
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<td></td>
<td></td>
<td>▪ Targeted product classes (e.g. if toxic, sensitizing, mutagenic, beta-lactams, sensitive to light, temperature and/or humidity)</td>
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<tr>
<td></td>
<td></td>
<td>▪ Targeted production capacity</td>
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End of section: Phase I, Site

Site compliant with WHO GMP, but quality management systems (QMS) not in line with WHO GMP

Section 1.2: Phase I, QMS

<table>
<thead>
<tr>
<th>Phase/Ref. No.</th>
<th>Key quality element</th>
<th>Actions for implementation</th>
<th>Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1</td>
<td>Quality assurance</td>
<td>Development of an organizational structure (organogram) within the company outlining hierarchy, functional levels and reporting lines. The organizational structure has to ensure a separation of quality assurance/control from production.</td>
<td>Authorized organizational charts in place</td>
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</table>

End of section: Phase I, QMS

Note: During the improvement of site and QMS at already existing pharmaceutical manufacturers towards WHO GMP, activities outlined in Sections 1.1 and 1.2 should be conducted concurrently.

Site and QMS identified as main technical challenges in Kenya compliant with WHO GMP

Section 2: Phase II

<table>
<thead>
<tr>
<th>Phase/Ref. No.</th>
<th>Key quality element</th>
<th>Actions for implementation</th>
<th>Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Complaints</td>
<td>Development and implementation of a documented system regarding handling, investigation, corrective and preventive actions of complaints containing:</td>
<td>Documented system for handling, investigation, corrective and preventive actions of complaints in place and implemented</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Responsible person(s) and responsibilities</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>▪ Procedures to be followed for handling, investigation, corrective and preventive actions of complaints including timelines</td>
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</tbody>
</table>

End of section: Phase II

Completion: Site and QMS in compliance with WHO GMP
Safety news

Safety warnings

Loperamide: Serious heart problems with high doses
United States of America – The FDA has warned that higher than recommended doses of the anti-diarrhoea medicine loperamide (Imodium® and associated names), including through abuse or misuse, can cause serious and potentially fatal heart problems. The maximum FDA-approved doses for adults are 8 mg per day for over-the-counter use and 16 mg per day for prescription use. The risk may be increased when high doses of loperamide are taken with medicines that inhibit CYP3A4, CYP2C8, and/or P-glycoprotein.

Health professionals should make their patients aware of this risk and should instruct them to seek medical attention immediately if they experience symptoms of heart problems. Loperamide toxicity should be suspected in case of unexplained QT interval prolongation, torsades de pointes or other ventricular arrhythmias, syncope and cardiac arrest. In such cases loperamide should promptly be discontinued and necessary therapy started. For some cases of torsades de pointes in which drug treatment is ineffective, electrical pacing or cardioversion may be required.

► FDA Drug safety communication, 7 June 2016.

Saxagliptin, alogliptin: heart failure
United States of America – An FDA safety review has found that type 2 diabetes medicines containing saxagliptin (Onglyza®, Kombiglyze®) and alogliptin (Nesina®, Kazano®, Oseni®) may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. New warnings have been added to the product information for these medicines. Health care professionals should consider discontinuing saxagliptin- or alogliptin-containing medicines in patients who develop heart failure, and should monitor their diabetes control to see whether other antidiabetic medicines are required. (1)

The EU product information for saxagliptin-containing medicines states that caution is warranted in patients with risk factors such as a history of heart failure or moderate to severe renal impairment. It also states that patients should be advised of the characteristic symptoms of heart failure and to report such symptoms immediately to their health care professionals. For alogliptin the EU product information includes a warning that experience of alogliptin use in clinical trials in patients with moderate to severe congestive heart failure is limited and caution is warranted in these patients. (2)

► (1) FDA Drug safety communication, 5 April 2016.

(2) EMA Product information for Vipidia®, Annex 1: Summary of product characteristics, last updated 3 February 2015.
**Fluconazole: risk of miscarriage**

United States of America – The FDA is evaluating the results of a Danish study that point to a possible increased risk of miscarriage with the use of oral fluconazole (Diflucan® and generics), an antifungal medicine used to treat yeast infections. The Agency is also reviewing additional data. Guidelines issued by the U.S. Centers for Disease Control and Prevention (CDC) recommend only topical – not oral – antifungal products in pregnant women, even in case of persisting or recurring infections that necessitate prolonged treatment. The current FDA product information states that data available from human studies suggest no increased risk in pregnant women exposed to a single 150 mg dose of oral fluconazole. However, high doses (400-800 mg/day) taken repeatedly have resulted in reports of abnormalities at birth. In the Danish study, most of the oral fluconazole use appeared to be one or two doses of 150 mg. Until the review is complete, the FDA advises cautious prescribing of oral fluconazole in pregnancy. (1)

The prescribing information for fluconazole-containing medicines in the EU cautions against use during pregnancy. This is based on reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers received long-term treatment with high doses of fluconazole for fungal infections. (2)

► (1) FDA. Drug safety communication, 26 April 2016.

(2) Diflucan® 150 mg capsules. Summary of product information. Last updated on UK electronic Medicines Compendium (eMC) on 6 November 2015.

**Imatinib, dasatinib, nilotinib, bosutinib, ponatinib: hepatitis B reactivation**

European Union, Canada – New wording has been included in product information for products containing BCR-ABL tyrosine kinase inhibitors (including imatinib, dasatinib, nilotinib, bosutinib and ponatinib) to warn about the risk of hepatitis B reactivation in patients who are chronic carriers of this virus. Some reported cases have resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

BCR-ABL tyrosine kinase inhibitors are approved in the EU to treat certain forms of leukaemia, lymphoma and other conditions. Patients should be tested for hepatitis B virus infection before treatment with a BCR-ABL tyrosine kinase inhibitor is initiated. Patients carrying the hepatitis B virus who need treatment should be closely monitored during treatment and for several months thereafter.

► EMA. Extracts from PRAC recommendations on signals. 25 February 2016.

Health Canada Advisory, 4 May 2016.


**Trametinib: gastrointestinal perforation and colitis**

United Kingdom – Following a review of data on trametinib (Mekinist®) by European regulators, the MHRA has advised health professionals to use this medicine with caution in patients with risk factors for gastrointestinal perforation, such as gastrointestinal metastases, diverticulitis or concomitant use of medicines that can cause gastrointestinal perforation. Patients should be advised...
to seek urgent medical attention if they develop severe abdominal pain.

Trametinib is authorized in Europe either as monotherapy or in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.


**Aflibercept: osteonecrosis of the jaw**

United Kingdom – The MHRA has advised that a dental examination and appropriate preventive dentistry should be considered before starting treatment with the anti-cancer medicine aflibercept (Zaltrap®). During treatment, patients should maintain good oral hygiene; receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain or swelling to their health care provider.

This follows reports of cases of osteonecrosis of the jaw in patients who have been treated with aflibercept. Patients who have received prior or concurrent treatment with an intravenous bisphosphonate may be at particular risk. In these patients, invasive dental procedures should be avoided where possible.

Aflibercept is also the active ingredient in Eylea® intravitreal injection, which is authorized for treatment of macular degeneration. Osteonecrosis of the jaw has not been identified as a risk associated with Eylea®.


**Idelalisib: infections and other serious adverse events**

Following observations of serious adverse events – mostly infections – in clinical trials involving the cancer medicine idelalisib (Zydelig®) several regulatory safety reviews have been initiated (see page 208), and the following announcements have been made.

European Union – The EMA has recommended new interim safety measures for idelalisib. All patients should receive prophylaxis for Pneumocystis jirovecii pneumonia during treatment and should be monitored for respiratory signs and symptoms and for cytomegalovirus infection. Patients should be monitored for neutropenia. In case of moderate or severe neutropenia treatment may need to be interrupted. Idelalisib should not be started in patients with an ongoing systemic infection, or in previously untreated patients with chronic lymphocytic leukaemia (CLL) whose cancer cells have certain genetic mutations. Ongoing first-line treatment for CLL should only be continued if the benefits outweigh the risks for the individual patient. (1)

United States of America – The FDA has reminded health professionals that idelalisib is not approved in the United States for previously untreated CLL. (2)

Canada – Health Canada has recommended that idelalisib should not be used for first line treatment of CLL. The product monograph will be updated to reflect this new information. (3)

(2) FDA Drug alert, 14 March 2016.
(3) Health Canada Advisory, 3 May 2016.
Thalidomide: viral reactivation and pulmonary hypertension

European Union – Product information for the anti-myeloma medicine thalidomide is being updated to include warnings on the risk of viral reactivation and pulmonary hypertension. Information for health care professionals is scheduled to be disseminated in late June 2016.

Cases of viral reactivation, including some serious cases, have been reported following treatment with thalidomide, particularly in patients previously infected with the herpes zoster or hepatitis B viruses. Recommendations to mitigate this risk are similar to those for pomalidomide (see below).

Cases of pulmonary hypertension, including some fatal cases, have also been reported following treatment with thalidomide. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease before and during thalidomide therapy.

► EMA Opinions on safety variations/PSURs. EMA/76604/2016. 27 May 2016.

Pomalidomide: hepatitis B reactivation

United Kingdom – A review of clinical studies and reported suspected adverse drug reactions by European medicines regulators has concluded that pomalidomide (Imnovid®) can cause hepatitis B reactivation. Hepatitis B virus status should be established before starting treatment with pomalidomide. If a patient tests positive, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Previously infected patients should be closely monitored for signs and symptoms of active infection throughout pomalidomide treatment.

Pomalidomide in combination with dexamethasone is used to treat adult patients with relapsed and refractory multiple myeloma. Cases of hepatitis B reactivation, some of which progressed to hepatic failure, have been reported in less than 1 of 1 000 patients treated, with most reports occurring during the first treatment cycle.


Olanzapine: rare but serious skin reactions

United States of America – The FDA has warned health professionals and the public that the antipsychotic medicine olanzapine (Zyprexa®, Zyprexa Zydis®, Zyprexa Relprev® , Symbyax® and generics) can cause a rare but serious and potentially fatal skin reaction known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). A new warning has been added to the product information for all olanzapine-containing products.

Olanzapine is used to treat schizophrenia and bipolar disorder. Prescribers should explain the signs and symptoms of severe skin reactions to their patients and instruct them to seek medical care if they develop a fever with a rash and swollen lymph glands, or swelling in the face. Health professionals should stop treatment with olanzapine immediately if DRESS is suspected. (1)

European Union – European medicines regulatory authorities have reviewed cases of DRESS in patients taking olanzapine. An update of the product information for olanzapine-containing medicines has been recommended to list DRESS as a possible side effect. The
condition is very rare and will be listed in the product information as occurring at an unknown frequency. (2)

▶ (1) FDA Drug safety communication. 10 May 2016.

(2) EMA. New product information wording – Extracts from PRAC recommendations on signals. EMA/PRAC/259913/2016, 28 April 2016.

Known risks

Metformin: expansion of use in kidney impairment

United States of America – The FDA has reviewed available data and has expanded the use of the anti-diabetic medicine metformin to patients with mild renal impairment and certain patients with moderate renal impairment. Metformin was previously contraindicated in the U.S. in all patients with renal impairment because of the risk of lactic acidosis.

The FDA recommends that the glomerular filtration rate-estimating equation (eGFR), rather than the blood creatinine concentration, should be used to assess kidney function. Metformin is contraindicated in patients with an eGFR <30 mL/minute/1.73 m², and is not recommended in patients with an eGFR of 30-45 mL/minute/1.73 m². The eGFR should be monitored at least annually, and more often in patients at increased risk of renal impairment. Metformin should be stopped if the eGFR falls below 30 mL/minute/1.73 m², and treatment discontinuation considered if it falls below 45 mL/minute/1.73 m².

If an iodinated contrast imaging procedure is to be performed in certain at-risk patients, health professionals should stop metformin, re-evaluate the eGFR 48 hours after the procedure, and re-start metformin if renal function is stable.

▶ FDA Drug safety communication. 8 April 2016.

Aspirin-containing antacids: serious bleeding

United States of America – The FDA has warned consumers about the risk of serious bleeding when using over-the-counter aspirin-containing antacid products. Despite existing warnings in the product information, reports continue to be received of these serious adverse events. The FDA plans to convene an advisory committee of external experts to advise on whether additional regulatory actions are needed.

▶ FDA Drug safety communication. 6 June 2016.

Oral ketoconazole: use only for serious fungal infections

United States of America – The FDA has reminded health care professionals not to prescribe oral dosage forms of the antifungal medicine ketoconazole (Nizoral® and other names) for skin and nail fungal infections. Since 2013 oral ketoconazole is no longer approved to treat these conditions as it carries a risk of serious liver damage, adrenal gland problems and harmful interactions with other medicines and has been linked to one patient death since the labelling change. Oral ketoconazole should be used only for serious fungal infections when no other effective therapy is available. Yet, a 2015 safety review found that ketoconazole tablets continue to be prescribed for skin and nail fungal infections.

▶ FDA Drug safety communication. 19 May 2016.
**Opioids: enhanced warnings**

**United States of America** – The FDA has announced new class-wide warnings for immediate-release opioid pain medications related to risks of misuse, abuse, addiction, overdose and death, and a warning that chronic use of opioids during pregnancy can result in neonatal opioid withdrawal syndrome (NOWS), which may be life-threatening for the infant if not recognized and treated.

New safety warnings have also been added to all prescription opioid medications to inform prescribers and patients of additional risks related to opioid use. Clearer information has been included about the indications, dosage, interactions with other medicines including the risk of serotonin syndrome, and about the effects of opioids on the endocrine system, including adrenal insufficiency and androgen deficiency.

► *FDA News release, 22 March 2016.*

**Aripiprazole: impulse control disorders**

**United States of America** – The FDA has approved changes to the product information of the mental health drug aripiprazole (Abilify®, Abilify Maintena®, Aristada®) to warn about compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex reported with this medicine. Patients should be informed of these risks and closely monitored. *(1)*

This follows a similar risk communication issued by Health Canada in 2015 *(2).*

Product information approved in the EU *(3)* lists pathological gambling as a side effect which can occur in patients who have no history of gambling, and advises that patients treated with this medicine who have a history of pathological gambling should be monitored carefully. Altered or increased sexual interest (in up to 1 in 100 people) and weight gain are also listed as side effects.

► *(1) FDA Drug safety communication, 3 May 2016.*

► *(2) Health Canada Advisory, 2 November 2015.*

► *(3) EMA Product information for Abilify®, Annex 1: Summary of product characteristics, updated 23 May 2016.*

**Restrictions**

**Fluoroquinolones: restricted use in certain uncomplicated infections**

**United States of America** – The FDA has approved labelling changes for fluoroquinolone antibacterial medicines (moxifloxacin, ofloxacin, ciprofloxacin) to limit their use in sinusitis, bronchitis and uncomplicated urinary infection. In treating these conditions, systemic fluoroquinolones should be reserved for patients who do not have alternative treatment options. The reason for this restriction is the risk of a number of disabling and potentially permanent serious side effects that can occur together.

The FDA had communicated safety information about systemic fluoroquinolone drugs in 2008 and 2013. An FDA safety review has shown that systemically used fluoroquinolones are associated with adverse effects that can involve the tendons, muscles, joints, nerves and central nervous system. Health care professionals should stop systemic fluoroquinolone treatment immediately if a patient reports serious side effects and switch to a non-fluoroquinolone antibacterial drug to complete the patient’s treatment course.

► *FDA Drug safety communication, 13 May 2016.*
Withdrawals from the market

Meprobamate: last marketing authorization cancelled in U.K.
United Kingdom – Following a 2012 EU-wide review of the sedative medicine meprobamate, the remaining licence holder in the UK has ceased manufacturing and the licence will be cancelled by the end of 2016. (1)

In 2012 the EMA had recommended that marketing authorizations for oral medicines containing meprobamate should be suspended in the EU due to serious side effects seen with the medicine (2). The suspension was implemented gradually to avoid the risk of severe withdrawal symptoms in patients stopping treatment abruptly.
► (1) MHRA Drug Safety Update vol 9 issue 9, April 2016: 8.
(2) EMA Press release, 20 January 2012.

Fusafungin-containing sprays: rare but serious allergic reactions
European Union – The EMA’s Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed a recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC) to revoke the marketing authorizations for fusafungine-containing products in the EU.

Fusafungine is an antibiotic and anti-inflammatory used in nose and mouth sprays to treat upper airway infections including common cold. The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has found that fusafungin-containing sprays can cause rare but serious, potentially life-threatening allergic reactions, and no measures have been identified to sufficiently reduce or manage this risk. The evidence of beneficial effects of fusafungine is weak. Taking into account the mild and self-limiting nature of upper airway infections such as rhinopharyngitis, the benefits of fusafungine were not considered to outweigh the risks. In addition, it could not be ruled out that fusafungine may promote antibiotic resistance.
► EMA Press release, 1 April 2016.

Veterinary drug carbadox: to be removed from the U.S. market
United States of America – The FDA has taken steps towards rescinding its approval of the use of the veterinary drug carbadox to treat pigs, because the drug may leave trace amounts of a carcinogenic residue. A preliminary risk characterization had indicated that there could be a potential risk to human health from ingesting pork, especially pork liver, derived from carbadox-treated pigs.

Carbadox was first approved in the U.S. in the early 1970s to control swine dysentery and bacterial swine enteritis. It has also been used to promote weight gain and feed efficiency.
► FDA News release, 8 April 2016.

Unchanged recommendations

Recombinant factor VIII products: no difference in risk of antibody formation
European Union – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has published a summary report of a meta-analysis designed to assess the risk of inhibitors (antibodies) against individual recombinant factor VIII products developing in previously untreated
patients with severe haemophilia A. Specifically, the review concluded that overall, the currently available evidence does not confirm an increased risk associated with Kogenate® Bayer/ Helixate® NexGen, compared with other products. The conclusions are consistent with those of a 2013 PRAC review of Kogenate® Bayer/Helixate® NexGen.

► EMA News, 13 May 2016.

### Meningococcal vaccine: no new safety concerns

**Australia** – The TGA has been closely monitoring reports of adverse events following immunisation with Bexsero® meningococcal B vaccine, specifically those relating to fever in infants and children. Fever is a potential risk factor for the development of a seizure. The TGA’s monitoring activities have found no new or unexpected safety issues. All the adverse events observed during the monitoring were identified in the pre-market evaluation, and the numbers of reports were within expectations. Health professionals have been reminded that the Australian Technical Advisory Group on Immunisation has recommended the prophylactic use of paracetamol with every dose of Bexsero® administered to children less than two years old.

► TGA final update, 22 March 2016.

### Inhaled corticosteroids for COPD

**European Union** – The EMA has reviewed the known risk of pneumonia with inhaled corticosteroids for chronic obstructive pulmonary disease (COPD). The review concluded that the benefits of these medicines continue to outweigh their well-known risk of pneumonia, which occurs in 1–10 of 100 patients treated. No conclusive evidence was found of any differences in the risk of pneumonia between products.

No changes are recommended in the use of inhaled corticosteroids to treat COPD. Health professionals should however be vigilant for signs and symptoms of pneumonia, which overlap with those of exacerbations of COPD.

► EMA Press release, 29 April 2016.
## Medicines safety reviews started

<table>
<thead>
<tr>
<th>Product</th>
<th>Use</th>
<th>Concerns</th>
<th>Reviewing authority reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin (Vokanamet®, Invokana®)</td>
<td>Treatment of type 2 diabetes</td>
<td>Increase in amputations, mostly affecting toes, observed in an ongoing clinical trial. The scope of the EMA review may be extended to other SGLT2 inhibitors at a later stage.</td>
<td>EMA reviews diabetes medicine canagliflozin. EMA/267042/2016, 15 April 2016. FDA Drug safety communication, 18 May 2016. TGA Safety advisory, 7 June 2016.</td>
</tr>
<tr>
<td><em>Escherichia coli</em> bacteria cells and autolysate (Symbioflor 2® and associated names)</td>
<td>Treatment of diseases affecting the stomach and gut, including irritable bowel syndrome</td>
<td>Effectiveness not adequately demonstrated</td>
<td>EMA Article 31 referral - Review started, 1 April 2016.</td>
</tr>
<tr>
<td>Ticagrelor (Brilinta®)</td>
<td>Prevention of blood clots in adult patients with acute coronary syndromes</td>
<td>Placed on New Zealand early warning monitoring scheme due to possible safety concern regarding depression and suicidality, suggested by reports in the WHO database.</td>
<td>Medsafe Monitoring communication, 1 March 2016.</td>
</tr>
<tr>
<td>Vancomycin-containing products</td>
<td>Treatment of serious infections with Gram-positive bacteria resistant to other antibiotics</td>
<td>Need for review of the benefit-risk balance and consideration of updates to product information to promote appropriate use in the context of the fight against antimicrobial resistance.</td>
<td>EMA Article 31 referral - Review started, 1 April 2016.</td>
</tr>
<tr>
<td>Fluconazole Diflucan® and generics</td>
<td>Treatment of yeast infections, treatment of cryptococcal meningitis</td>
<td>Possible increased risk of miscarriage. The FDA advises cautious use of fluconazole in pregnancy (see also page 200).</td>
<td>FDA Drug safety communication, 26 April 2016.</td>
</tr>
<tr>
<td>Direct-acting antivirals for hepatitis C (Exviera®, Harvoni®, Olysio®, Sovaldi®, and Viekirax®)</td>
<td>Treatment of chronic hepatitis C infection</td>
<td>Hepatitis B reactivation. In April 2016 the review was extended to also evaluate the risk of liver cancer. In Japan, updates have been recommended to the product information for hepatitis C direct-acting antivirals to include the risk of hepatitis B reactivation.</td>
<td>EMA Article 20 referral - Review started, 18 March 2016. PMDA Summary of investigation results, 18 May 2016.</td>
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Continued
Non-compliance with good practices

**Alkem Bioequivalence Centre, India**

**European Union** – The EMA has started a review of medicines for which studies have been conducted at the Alkem Laboratories Ltd site in Taloja, Mumbai, India. This follows a good clinical practice (GCP) inspection of this site which raised concerns regarding study data used to support the marketing authorization applications of some medicines in the EU. The inspection was carried out jointly by the German and Dutch authorities in March 2015 in the context of a routine evaluation of applications for nationally authorized medicines. The EMA will now determine which medicines are concerned and will review the available data to determine whether any action is necessary to protect public health.

► EMA Article 31 referral - Review started, 1 April 2016.

**Semler Research Center Pvt Ltd, India**

**Geneva** – The WHO Prequalification Team (PQT) has issued a notice of concern about serious observations made during an inspection of Semler Research Center’s JP Nagar site and Sakar Nagar clinical unit on 27–31 January 2015 and a follow-up inspection on 2-5 December 2015, stating that some of the observations are indicative of manipulation of several studies over an extended period of time. Manufacturers of affected prequalified products have been asked to submit risk assessments with proposed corrective and preventive actions within 30 days (1).

**United States of America** – The FDA has notified pharmaceutical companies that clinical and bioanalytical studies conducted by Semler Research Center Pvt Ltd in Bangalore, India, are unacceptable.
Safety news

and need to be repeated. The notification was made as a result of an FDA inspection of Semler’s bioanalytical facility on 29 September–9 October 2015, which found significant instances of misconduct including the substitution and manipulation of study subject samples. (2)

European Union – The EMA has started a review of medicines for which studies have been conducted at Semler Research Centre Private Ltd, as the findings from the FDA and WHO inspections call into question the reliability of data generated at Semler, including data used to support marketing authorization applications in the EU. (3)

► (1) WHO Notice of Concern, 12 April 2016.
(2) FDA Notification to pharmaceutical companies, 20 April 2016.
(3) EMA. Semler – Article 31 review started. 29 April 2016.

Anuh Pharma API manufacturing site, India

Geneva – The WHO Prequalification team has temporarily de-listed two prequalified active pharmaceutical ingredients (API) manufactured by Anuh Pharma Ltd at its facility in Boisar, India (1). This follows a statement of non-compliance with good manufacturing practice (GMP) issued by the French medicines regulatory authority (2). Anuh Pharma has requested WHO to conduct an inspection to verify GMP compliance at the site.

WHO has advised finished product manufacturers to undertake a risk analysis of API batches already purchased, and to halt sourcing of further batches of pyrazinamide from Anuh Pharma until they are reinstated on the WHO prequalification list. National regulatory agencies and procurers should consider both the specific risk posed by an individual FPP batch and the need to maintain continuity of supply.

(2) GMP certificates and non-compliance reports issued by medicines regulatory authorities in the European Economic Area (EEA) are publicly available at: http://eudragmdp.ema.europa.eu/inspections/gmpc/index.do

Falsified product alert

Injectable carmustine

United States of America – The FDA has warned health professionals that a falsified version of the FDA-approved cancer drug carmustine for injection 100 mg (BiCNU®) has been detected in some countries outside the U.S. The authentic product is approved in the U.S. to treat different types of brain cancer, multiple myeloma, and lymphoma (Hodgkin’s and non-Hodgkin’s). The genuine product is manufactured by Emcure Pharmaceuticals Ltd.

The product is available as a vial of BiCNU® and dehydrated alcohol co-packaged together. The best way to distinguish the genuine from the falsified product is to look at the BiCNU® vial inside the packaging. The authentic product has a blue flip top while the falsified product has a grey flip top. The National Drug Code (NDC) number on the authentic product vial should end with -31, not -41. Photographs of an authentic and a falsified product, and a list of lot numbers, batch vial, manufacturing dates, and expiration dates found on falsified products, are available on the FDA web site.

► FDA Drug alert, 12 May 2016.
TGA Safety advisory, 23 May 2016.
Regulatory news

Pre-market assessment

EMA offers routine parallel scientific advice

European Union – The EMA has published a report on its pilot on parallel scientific advice allowing pharmaceutical companies to receive simultaneous feedback on their development plans for new medicines from both regulators and health-technology-assessment (HTA) bodies. A total of 63 parallel scientific advice procedures were completed from July 2010 to December 2015.

Parallel scientific advice helps to ensure that clinical trials are designed to generate the evidence needed for both regulatory and health technology assessment. Assessment of both the benefit-risk balance and the added value of a new medicine at the same time can reduce delays between its marketing authorization and decisions on reimbursement.

The procedure is routinely offered by EMA since the end of the pilot. A best practice guide has also been published. (1)

A report by the EMA and the European network for Health Technology Assessment (EUnetHTA) highlights the key achievements of work done in 2012–2015 and future collaborative approaches for collection of robust post-authorization data, rapid EUnetHTA relative effectiveness assessments and joint discussions on the therapeutic indications of medicines. (2)

EMA guidance on patient-reported outcomes for anticancer medicines

European Union – The EMA has published new guidance on how patient-reported outcome data should be integrated in oncology clinical trials.

Patient-reported outcomes include any data directly reported by a patient based on his or her perception of a disease and its treatment. They provide information on a patient’s quality of life, symptoms, treatment adherence or satisfaction with care. The guidance acknowledges the importance of bringing the perspective of patients to the assessment of benefits and risks of cancer medicines. Patient-reported outcomes and health-related quality of life measures complement the range of traditional indicators of efficacy of an oncology medicine and can reflect both positive and negative patient experiences.

Ten years of EMA’s small and medium enterprise initiative

European Union – Ten years after the EMA’s small and medium enterprise (SME) regulation came into force, the Agency has published a report that highlights the importance of SMEs in pharmaceutical innovation and trends observed in the past ten years.

SME applications account for approximately 10–15% of all marketing authorization applications for new medicines. Of the medicines developed by SMEs and approved in the past ten years, more than half contained a new active substance, and 42% were for
orphan medicines. SMEs are increasingly making use of scientific advice during product development, including the parallel scientific advice with health-technology-assessment bodies that deal with reimbursement decisions.

By the end of 2015, 1619 companies from across the EU were listed in a public register maintained by EMA to enable networking and increase transparency.


### Access to advanced therapies

**European Union** – The EMA has published a report from a multi-stakeholder expert meeting held in May 2016 to explore possible ways to foster the development and authorization of advanced therapy medicinal products in Europe.

Advanced therapies comprise gene therapies, tissue-engineered products and somatic cell therapies. These medicines could open up new treatment options for a wide range of conditions, including some where conventional approaches are inadequate. However, since EU legislation on ATMPs entered into force in 2008, only five such products have been authorized. The meeting report summarizes the ideas and solutions proposed on the subject by a wide range of stakeholders. The proposals are under discussion by EMA, its committees and national regulatory authorities with a view to determine concrete actions over the next few months.

► EMA Press release, 3 June 2016.

### FDA simplifies request process for compassionate use products

**United States of America** – The FDA has put into place a streamlined process for doctors to request expanded access, also called “compassionate use”, to investigational drugs and biologics for their patients. A simplified application form (Form FDA 3926) has been released, together with step-by-step instructions on how to complete it. In addition, the FDA has provided two guidance documents with explanations about expanded access and how to request it, and about how patients may be charged for investigational products.

► FDA News release, 2 June 2016.

### Information-sharing

**Guide to key EMA information on human medicines**

**European Union** – The EMA has released a new guide (1) that describes the different types of information published by the Agency on human medicines during of their life span, from early development through initial evaluation, adoption of positive or negative opinions, to post-authorization changes and safety reviews. Some best practice guidance for marketing authorization holders, applicants and third parties is provided in the guide to ensure accurate and timely communication. This is especially relevant for information which might be sensitive or which may generate significant public interest.

The guide includes an easy-reference annex with tables listing the document types produced by the Agency at different stages of a medicine’s life cycle, times
Post-marketing control

EMA adopts rules for public hearings on selected safety reviews

European Union – The EMA has adopted the final rules of procedure for public hearings to be held by its Pharmacovigilance Risk Assessment Committee (PRAC). The process and procedures will be tested in a dry run in July 2016.

Public hearings are a new tool for EMA to listen to the views and experiences of citizens regarding the supervision of medicines. Their legal basis is Article 107j of Directive 2001/83/EC.

Public hearings could take place as early as the fourth quarter of 2016, as soon as a relevant topic is identified. They will be held on a case-by-case basis in situations where the PRAC determines that the views of the public would bring added value to its review. They will complement existing channels of stakeholder engagement during the early stage of a safety review, enabling the PRAC to consider different risk minimization options in a wider public health context.

► EMA Press release, 15 April 2015.

FDA revises rule on reporting of veterinary antimicrobial sales

United States of America – The FDA has finalized a revised rule on the annual reporting requirements of sales and distribution of all antimicrobials for use in animals intended for human consumption or food-producing animals. In addition to overall estimates of antimicrobials sales, companies are now required to provide estimates broken down by major food-producing species (cattle, swine, chickens and turkeys).

The new sales data will help the FDA to target its efforts to ensure judicious use of medically important antimicrobials.

► FDA News release, 10 May 2016.

Update on Japan’s data network on adverse drug reaction in children

Japan – The Ministry of Health, Labour and Welfare (MHLW) has provided an update on the “Children and Pharmaceuticals” Data Collecting Network Development Project in Japan. This project was conceived in 2012 to support safer use of medicines for children. A consolidated data collecting system has been put into place by the National Center for Child Health and Development, making use of networks such as the Japanese Association of Children’s Hospitals and related institutions. As of 29 February 2016, approximately 140 000 adverse drug reaction reports have been received from four children’s hospitals and 33 clinics. Ultimately, the system is to be implemented in 11 children’s hospitals and approximately 35 clinics. Further system development is under consideration.

► “Children and Pharmaceuticals” Data Collecting Network Development Project. Pharmaceuticals and Medical Devices Safety Information No. 331, March 2016:4-6.
Law enforcement

Operation Pangea IX highlights the dangers of buying medicines online

Lyon, France – Regulatory authorities of 103 countries participated in the International Operation Pangea IX, which took place from 30 May to 7 June 2016 as part of the Ninth Annual International Internet Week of Action. Coordinated by INTERPOL, Operation Pangea is an annual global cooperative effort aiming to combat the unlawful sale and distribution of illegal prescription medicines and medical devices on the Internet. This year’s operation was the largest of its kind so far. It led to the seizure of 170,340 shipments containing a total of 12.2 million potentially dangerous illicit medicines worth more than 53 million US$, as well as the suspension of 4,932 websites selling illicit pharmaceuticals.


Rational medicines use

India bans over 300 fixed-dose combinations

India – The Ministry of Health has banned 344 fixed-dose combinations contained in 1,600 brands worth 37 billion Indian Rupees (approximately 550 million US$) following recommendations of an expert committee formed to examine their safety and efficacy. The banned FDCs include cough syrup solutions, analgesic and antibiotic combinations and others, many of which are sold over the counter. (1)

Concerns about unapproved fixed-dose combinations in India have been supported by the findings published in a 2012 research report (2). The legal conundrum is that until 1988, FDCs were not considered as new drugs in India and therefore needed no approval. Even after 1988, manufacturing licences for thousands of FDC products were still issued legally by state controllers until 2002, when prior approval of the FDC by the central drug controller became mandatory. While the state governments can prohibit manufacture of drugs only if these are found to be falsified or if the manufacturer has violated any rules, the Central Government can ban drugs for reasons of public health. (3)

Public health supporters have welcomed the move, while manufacturers feel that they are unjustly punished when they have not contravened any laws. Nine years earlier, a similar government attempt could not be executed as the order was challenged in the Madras High Court. Commentators doubt that the ban can be implemented effectively. (4)

► (1) The Gazette of India. No. 608, 10 March 2016.
(2) McGettigan P et al. Use of Fixed Dose Combination (FDC) Drugs in India: Central Regulatory Approval and Sales of FDCs Containing Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Metformin, or Psychotropic Drugs. PLOS Medicine. Published online, 12 May 2015. http://dx.doi.org/10.1371/journal.pmed.1001826
(3) Talwar P. Irrational FDCs in India. E-drug post. 29 Jan 2015.
Under discussion

European Union – A European expert group has proposed further restrictions of the use of the last-resort antibiotic colistin in animals. The updated advice was provided following the discovery of a new mechanism of resistance in bacteria to colistin with potential for rapid spread. The comment period ended on 26 June 2016.

► EMA Press release, 26 May 2016.

European Union – The EMA has started a review of the guidelines on the safety of first-in-human clinical trials in cooperation with the European Commission and EU Member States. The review follows a tragic incident which occurred during a Phase I clinical trial in France in January 2016, leading to the death of one participant and hospitalization of five others. An agreed concept paper is expected by July 2016.


Canada – The Government of Canada is moving forward with mandatory reporting of medicines shortages. Prequalified contractors have been invited to submit proposals to develop and maintain an independent website for reporting of shortages.


Australia – The Advisory Committee on Medicines Scheduling met on 15 March 2016 to consider the large number of submissions received on the proposed up-scheduling of all over-the-counter codeine products to become prescription-only medicines. A TGA-commissioned independent review of low dose codeine-containing products is also being considered. A final decision is expected after June 2016.


United States of America – The FDA has issued draft guidance on evaluating the abuse deterrence of generic solid oral opioid products. This follows the agency’s final guidance for brand name opioids, which was issued in April 2015 as the first step to provide a framework for what studies were needed to evaluate a product’s ability to deter abuse. The period for public comment is 60 days.


United States of America – The FDA has issued three new draft guidance texts related to compounding of human medicines, describing the Agency’s proposed policies and application of the prescription requirement in section 503A of the Food, Drug, and Cosmetic Act and the definition of the term “facility” in section 503B of the Act. The period for public comment is 90 days.

► FDA Statement, 15 April 2016.

European Union – The EMA has released a draft reflection paper that outlines a framework for the extrapolation of clinical trial data from adults to children to support the authorization of new medicines for children. The paper was published ahead of a workshop held on the topic with experts and stakeholders in May 2016. The next version of the reflection paper is expected to be released for public consultation by end of July 2016.

► EMA News, 4 April 2016.

Canada – Health Canada has announced a proposed regulatory amendment to allow access to diacetylmorphine in chronic relapsing opioid dependence under its Special Access Programme (SAP). The period for public comment is 30 days.

Approved

Obeticholic acid for primary biliary cholangitis
Product name: Ocaliva®
Dosage form: Tablets
Class: Bile acid preparation;
ATC code: A05AA04
Approval: FDA (fast-track and orphan drug designations; accelerated approval)
Use: Treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as a single therapy in adults unable to tolerate UDCA.
Benefits: Reduction in alkaline phosphatase (ALP) level as a surrogate endpoint to predict clinical benefit. A confirmatory trial is ongoing to demonstrate improvement in survival and slower progression to cirrhosis.
► FDA News release, 31 May 2016.

Defibrotide sodium for rare complication in stem cell transplants
Product name: Defitelio®
Dosage form: Injection for intravenous use
Class: Antithrombotic agent;
ATC code: B01AX01
Approval: FDA (orphan drug designation, priority review)
Use: Treatment of adult and paediatric patients with hepatic veno-occlusive disease, also known as sinusoidal obstruction syndrome, with renal or pulmonary dysfunction following haematopoietic stem cell transplantation.
Benefits: First FDA-approved treatment for this rare, potentially fatal complication in patients who receive chemotherapy and haematopoietic stem cell transplantation.
Safety information: Risk of bleeding and allergic reactions. The product should not be used in patients with bleeding complications or those receiving systemic anticoagulant or fibrinolytic therapy.
► FDA News release, 30 March 2016.

Sofosbuvir/velpatasvir for hepatitis C virus infection
Product name: Epclusa®
Dosage form: Film-coated tablets
Class: Fixed-dose combination of two direct-acting antivirals: an NS5B inhibitor (sofosbuvir, ATC code J05AX15) and a novel NS5A inhibitor (velpatasvir).
Approval: EMA recommendation
Use: Treatment of chronic hepatitis C virus infection in adults
Benefits: When used with or without ribavirin, very high efficacy against all HCV genotypes including in patients with decompensated cirrhosis.
Note: The EMA has also recommended another hepatitis C fixed-dose combination product, elbasvir and grazoprevir (Zepatier®) for approval. This product was approved by the U.S. FDA in January 2016.

Pandemic influenza (H5N1) vaccine (live attenuated)
Product name: Pandemic influenza vaccine H5N1 MedImmune
Dosage form: Nasal spray (suspension)
Class: Influenza vaccine; ATC code: J07BB03
Approval: EMA recommendation
Use: Prophylaxis of influenza in an officially declared pandemic situation in children and adolescents from 12 months to less than 18 years of age. The vaccine should be used in accordance with official guidance.
Benefits: Ability to achieve an immune memory response for H5N1 starting as early as 4 weeks after vaccination and lasting for at least 4–5 years.
► EMA/CHMP Summary of opinion, 1 April 2016.
Venetoclax for chronic lymphocytic leukaemia
Product name: Venclexta®
Dosage form: Tablet for oral use
Class: BCL-2 inhibitor; ATC code (temporary): L01XX52
Approval: FDA (breakthrough therapy designation, priority review, accelerated approval; orphan drug designation)
Use: Treatment of patients with chronic lymphocytic leukaemia (CLL) with a 17p deletion who have received at least one prior therapy.
Benefits: Additional treatment option targeting a protein which supports cancer cell growth and is often overexpressed in CLL patients.
Safety information: Serious complications can include pneumonia, neutropenia with fever, fever, autoimmune haemolytic anaemia, anaemia and metabolic abnormalities known as tumour lysis syndrome. Live attenuated vaccines should not be given to patients taking venetoclax.
► FDA News release, 11 April 2016.

Daclizumab for relapsing multiple sclerosis
Product name: Zinbryta®
Dosage form: Solution for injection
Class: Humanised IgG1 monoclonal antibody, ATC code: L04AC01
Approval: EMA recommendation, FDA
Use: Treatment of adult patients with relapsing forms of multiple sclerosis
Benefits: Ability to reduce the relapse rate as well as the risk of 24-week confirmed disability progression.
Safety information: The most common side effects include elevations of liver enzymes and hepatic injury, cutaneous events, infections, gastrointestinal disorders and depression.
► EMA/CHMP Summary of opinion, 28 April 2016.

Ixekizumab for psoriasis
Product name: Taltz®
Dosage form: Injection
Class: Humanized monoclonal antibody binding to interleukin (IL)-17A; ATC code: L04AC13
Approval: FDA
Use: Treatment of psoriasis in patients who are candidates for systemic therapy, phototherapy or both.
Benefits: Inhibition of the inflammatory response that plays a role in the development of plaque psoriasis.
Safety information: Serious allergic reactions and development or worsening of inflammatory bowel disease have been reported.

Opicapone for Parkinson’s disease
Product name: Ongentys®
Dosage form: Hard capsules
Class: Peripheral, selective and reversible COMT inhibitor
Approval: EMA recommendation
Use: Adjunctive therapy to preparations of levodopa/DOPA decarboxylase inhibitors (DDCIs) in adult patients with Parkinson’s disease and end-of-dose motor fluctuations who cannot be stabilized on those combinations.
Benefits: Ability to decrease off-time (time when patients are severely restricted by their symptoms) and to increase on-time without troublesome dyskinesia.
► EMA/CHMP Summary of opinion, 28 April 2016.

Pimavanserin for symptoms associated with Parkinson’s disease
Product name: Nuplazid®
Dosage form: Tablets
Class: Atypical antipsychotic drug; ATC code (temporary): N05AX17
Approval: FDA (breakthrough therapy, priority review)
Use: Treatment of hallucinations and delusions associated with psychosis
experienced by some people with Parkinson’s disease

Benefits: First FDA-approved medicine to treat these symptoms associated with Parkinson’s disease.

Safety information: As all medicines in this class, the product carries a Boxed Warning about an increased risk of death in older people with dementia-related psychosis. No drug in this class is approved to treat patients with dementia-related psychosis.

► FDA News release, 29 April 2016.

Buprenorphine implant in opioid dependence

Product name: Probuphine®
Dosage form: Six-month implant
Class: Drug used in opioid dependence;
ATC code: N07BC01
Approval: FDA

Use: Treatment of opioid use disorder as part of a complete treatment programme that includes counselling and psychosocial support.

Benefits: Improved patient convenience compared with sublingual dosage forms

Safety information: The product must be prescribed and dispensed according to a Risk Evaluation and Mitigation Strategy programme because of the risks of surgical complications, accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.

► FDA News release, 26 May 2016.

Reslizumab for severe asthma

Product name: Cinqair®
Dosage form: Intravenous infusion for use every 4 weeks in a clinical setting
Class: Humanized interleukin-5 antagonist monoclonal antibody; ATC code: R03DX08
Approval: FDA

Use: In combination with other asthma medicines, for the maintenance treatment of severe asthma not controlled with conventional medicines in patients aged 18 years and older.

Benefits: Fewer asthma attacks, longer time to first attack and improved lung function compared with placebo

Safety information: Risk of serious hypersensitivity reactions.

► FDA News release, 23 March 2016.

Obiltoxaximab for inhalational anthrax

Product name: Anthim®
Dosage form: Injection for intravenous use
Class: Monoclonal antibody
Approval: FDA

Use: Treatment of inhalational anthrax in combination with appropriate antibacterial drugs.

Benefits: Neutralization of toxins produced by *Bacillus anthracis*; increased survival rates compared with placebo, and – when used in combination with antibacterials – higher survival rates than with antibacterial therapy alone. Anthrax is a potential bioterrorism threat.

Safety information: The product carries a Boxed Warning that the drug can cause hypersensitivity reactions including anaphylaxis.

Note: The product was approved under the FDA’s Animal Rule, which allows efficacy findings from adequate and well-controlled animal studies to support FDA approval when it is not feasible or ethical to conduct efficacy trials in humans.


Atezolizumab for bladder cancer

Product name: Tecentriq®
Dosage form: injection for intravenous use
Class: Programmed death-ligand 1 (PD-L1) inhibitor; first-in-class FDA-approved
Approval: FDA (breakthrough therapy, priority review, accelerated approval)

Use: Treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has worsened during or following platinum-containing chemotherapy, or within 12 months of receiving platinum-containing
Regulatory news

Approved chemotherapy either before or after surgical treatment.

**Benefits**: Additional treatment option for advanced or metastatic cases of this common type of bladder cancer.

**Safety information**: Potential to cause infection and severe immune-mediated side effects; potential to cause foetal harm.

**Note**: The FDA has also approved a diagnostic test to detect PD-L1 protein expression levels on patients’ tumour-infiltrating immune cells, helping to determine which patients may benefit most from treatment with atezolizumab.

► **FDA News release, 18 May 2016.**

### Migalastat for Fabry disease

**Product name**: Galafold®

**Dosage form**: Hard capsules

**Class**: A pharmacological chaperone designed to selectively and reversibly bind to certain mutant forms of the a-Gal A enzyme, resulting in restored enzyme activity.

**Approval**: EMA recommendation (orphan designation)

**Use**: Treatment of patients over 16 years with Fabry disease (alpha-galactosidase A deficiency) with an amenable mutation.

**Benefits**: More convenient treatment option for this rare genetic disorder than intravenous enzyme replacement therapy.

► **EMA Press release, 1 April 2016.**

### New gene therapy for ADA-SCID

**Product name**: Strimvelis®

**Dosage form**: Dispersion for infusion

**Class**: Gene therapy manufactured from a patient’s own immature CD34+ bone marrow cells into which a normal adenosine deaminase enzyme gene has been inserted.

**Approval**: EMA recommendation (orphan designation)

**Use**: Treatment of patients with adenosine-deaminase-deficient severe combined immunodeficiency (ADA-SCID), who have no matching donor for a stem cell transplant.

**Benefits**: First authorized treatment for ADA-SCID in the EU. Other options include stem cell transplants, which can be successful if there is a close match between the patient and the donor, and compassionate use enzyme replacement therapy, which may become less effective over time.

**Note**: ADA-SCID is an ultra-rare immune disorder. Children born with ADA-SCID have virtually no immunity to fight off everyday bacterial, fungal or viral infections.

► **EMA Press release, 1 April 2016.**

### Chlorhexidine digluconate to prevent umbilical infection in newborn infants

**Product name**: Umbipro®

**Dosage form**: Antiseptic gel

**Class**: Antiseptic agent; *ATC code*: D08AC02

**Approval**: EMA Article 58 procedure, providing a scientific opinion on the use of a medicine outside the EU.

**Use**: To cleanse the umbilical cord stump of newborn babies to prevent serious infection.

**Benefits**: Studies found a 20%–38% reduction in mortality in newborn infants delivered in community or primary care centres in resource-limited settings and a 24% to 75% reduction in umbilical cord infection where chlorhexidine was used.

**Notes**: WHO treatment guidelines recommend chlorhexidine for umbilical cord care for home births in regions with more than 30 deaths per 1 000 live births. It was identified by the United Nations as one of 13 life-saving commodities for women and children. The product was developed by the manufacturer in partnership with Save the Children in response to a call from the United Nations’ Commission on Life-Saving Commodities for Women and Children,
which is a part of the Every Woman, Every Child (EWEC) movement.

- **EMAnews** 29 April 2016.

Draft monographs enabling independent quality control testing of chlorhexidine digluconate solution and chlorhexidine digluconate topical solution have been proposed for inclusion in the *International Pharmacopoeia*. They are available for public comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects and will be reproduced in Issue 3 (2016) of *WHO Drug Information*.

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### Biosimilars

**Infliximab**

**Class:** Immunosuppressant; **ATC code:** L04AB02

**Use:** Treatment of rheumatoid arthritis, ulcerative colitis, Crohn’s disease, psoriatic arthritis, psoriasis and ankylosing spondylitis.

**Benefits:** Biosimilars can provide access to important treatment options for patients who need them.

1. **Active substance:** Infliximab
   **Product name:** Flixabi®
   **Dosage form:** Powder for concentrate for solution for infusion
   **Approval:** EMA recommendation (biosimilar to Remicade®)
   - [EMA/CHMP Summary of opinion, 1 April 2016](#).

2. **Active substance:** Infliximab-dyyb
   **Product name:** Inflectra®
   **Dosage form:** Intravenous injection
   **Approval:** FDA (biosimilar to, but not interchangeable with, Remicade®)
   **Notes:** Inflectra® is the second biosimilar to be approved in the United States, after filgrastim-sndz (Zarzio®). Inflectra® was authorized in the EU in 2013.
   - [FDA News release, 5 April 2016](#).

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### Brand name change

**Vortioxetine brand name changed to avoid confusion**

**Product name:** Trintellix® (formerly: Brintellix®)

**INN:** Vortioxetine

**Class:** Antidepressant; serotonin reuptake inhibitor (SSRI); **ATC code:** N06AX26

**Approval:** FDA

**Note:** The brand name was changed to avoid confusion with ticagrelor (Brilinta®), an antithrombotic agent. Trintellix® is expected to be available from June 2016. No other changes will be made to the product information or packaging, and the medicine is exactly the same.

- [FDA Drug safety communication, 2 May 2016](#).

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### Extensions of indications

**Crizotinib for certain rare, advanced non-small cell lung cancers**

**Product name:** Xalkori®

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

**Newly approved use:** Treatment of patients with advanced (metastatic) non-small cell lung cancer whose tumours have an ROS-1 gene alteration (first FDA-approved medicine for this indication).

- [FDA News release, 11 March 2016](#).

**Obinutuzumab for follicular lymphoma**

**Product name:** Gazyvaro®

**Approval:** EMA recommendation

**Newly approved use:** In combination with bendamustine, treatment of follicular lymphoma in patients previously treated with chemotherapy.

- [EMA Press release, 29 April 2016](#).
Investigational Zika test
United States of America – The FDA has announced the availability of an investigational test to screen donated blood in areas with active mosquito-borne transmission of Zika virus. This follows FDA guidance issued in February to reduce the risk of transfusion-transmitted Zika virus.

The FDA, the Office of the Assistant Secretary for Preparedness and Response/Biomedical Advanced Research and Development Authority and the Centers for Disease Control and Prevention are working to assist manufacturers with development of Zika virus screening tests to help protect the United States’ supply of blood and blood components during this outbreak.

► FDA News release, 30 March 2016.

Fluciclovine (\(^{18}\text{F})\) to detect prostate cancer recurrence
Product name: Axumin®
Dosage form: Injection
Class: Radioactive diagnostic agent
Approval: FDA
Use: For use in positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated prostate specific antigen (PSA) levels following prior treatment. Clinical correlation, which may include histopathological evaluation of the suspected recurrence site, is recommended.

Benefits: Accurate imaging approach for patients with suspected recurrent prostate cancer when the PSA is at low levels.

► FDA News release, 27 May 2016.

Gallium (\(^{68}\text{Ga})\) dotatate to detect rare neuroendocrine tumours
Product name: Netspot®
Dosage form: Injection for intravenous use
Class: Diagnostic radiopharmaceutical
Approval: FDA (orphan drug designation; priority review)
Use: To help locate somatostatin receptor-positive neuroendocrine tumours in adults and children. Findings may need to be confirmed by histopathology or other assessments.

Benefits: Useful method to locate neuroendocrine tumours, to inform planning of therapy.

► FDA News release, 1 June 2016.

Veterinary drug
Pegbovigrastim to reduce the incidence of mastitis
United States of America, Canada – The FDA and Health Canada have announced the simultaneous approval of pegbovigrastim injection (Imrestor®), an innovative veterinary drug that restores immune response and reduces and reduces the incidence of clinical mastitis of dairy cows and replacement dairy heifers.

Clinical mastitis is the inflammation of the mammary gland and udder tissue. Mastitis is a common disease in dairy cattle. Pegbovigrastim is expected to reduce reliance on other drugs, including antimicrobials, to treat mastitis infections.

Pegbovigrastim is the first simultaneously reviewed and approved animal drug for use in food-producing animals, and the fourth animal drug approved under the Canada–United States Regulatory Cooperation Council (RCC).


FDA Center for Veterinary Medicine (CVM) update, 29 March 2016.
Publications and events

Access to medicines

**WHO submission to the UN High-Level Panel**

**Geneva** – WHO has made a submission to the UN Secretary-General’s High-Level Panel on Access to Medicines to recommend solutions to remedy the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies. The submission presents WHO’s experience and a number of ongoing WHO projects to foster the development of priority health products, including the WHO/DNDi Global Antibiotic R&D Partnership, and makes a number of suggestions for possible areas of action to the Panel.


WHO Public health, innovation, intellectual property and trade. UN Secretary-General’s High-Level Panel on Access to Medicines [web page].

**Regulatory approaches to make medicines more affordable**

**European Union** – In an article published in the *New England Journal of Medicine*, representatives of European regulatory authorities discuss possible regulatory interventions to facilitate continued access to safe and effective medicines in health systems at affordable prices. The authors argue that although the pricing of medicines is clearly out of their remit, regulators cannot ignore the current debate on the cost of medicines. They propose five main ways how regulators can make a contribution to affordable health care: 1) Enable the rapid approval of generics and biosimilars; 2) ensure that medicines comparable to already approved ones continue to come on the market, thus increasing competition; 3) encourage clinical trials that demonstrate safety and efficacy and also provide data to guide reimbursement decisions; 4) facilitate the collection of post-approval data that are important for payers, for example data on outcomes for patients; and 5) foster new models for research and development enabling companies to reduce the price of their medicines.

▶ EMA News, 12 May 2016.


**UNITAID discussion paper on affordability of essential medicines**

**Geneva** – UNITAID has published a discussion paper that assesses the affordability of medicines and biologicals to treat hepatitis C, cancer and multi drug-resistant tuberculosis and proposes options for making them more affordable through price negotiations, voluntary licensing, patent pooling, and use of TRIPS flexibilities. The report emphasizes that the recent shifts in the WHO Essential Medicines paradigm demand a bold approach to avoid unnecessary delays in
making these medicines available to the populations in need.

► **Ensuring that essential medicines are also affordable medicines: challenges and options. Discussion paper.** Geneva: WHO (Acting as the host organization for the Secretariat of UNITAID), 2016.

**Intellectual property and local medicines production**

**Geneva** – A new WHO study on the role of intellectual property in medicines production sets out strategies and options to facilitate local production in developing countries. Using practical examples and patent landscapes, the report describes the options available to countries with a generic pharmaceutical industry to design an intellectual property system that is favourable for local production and potentially for public health.

The report contains detailed patent information on atazanavir, raltegravir, imatinib, sitagliptin, pegylated interferon alfa-2a, and human papillomavirus vaccine (Gardasil®).

► **WHO. The role of intellectual property in local production in developing countries - Opportunities and challenges.** Geneva, World Health Organization: 2016.

**GlaxoSmithKline announces new approach to patents**

Ahead of the meeting of the UN High Level Panel on Access to Medicines, GlaxoSmithKline (GSK) has announced its new and more flexible approach to patents and intellectual property to increase access to medicines. The company plans to use a graduated approach to filing and enforcing patents depending on a country’s economic maturity, seeking full patent protection only in high income countries, upper middle income countries and G20 countries. Additionally, GSK intends to commit its future portfolio of cancer treatments to patent pooling and will explore the concept with the Medicines Patent Pool (MPP). GSK would be the first company to licence cancer medicines to the patent pool. GSK will also work towards making information about its current and future patent portfolio freely available. (1)

The Union for Affordable Cancer Treatment (UACT) has welcomed the announcement, stating that it is “significant and encouraging” that GSK is seeking collaboration with the MPP, a public health-driven licensing mechanism with a proven track record. (2)

(2) UACT Statement, 6 April 2016.

**Study shows hepatitis C medicines prices are globally unaffordable**

A comparative study of prices and affordability of sofosbuvir and ledipasvir/sofosbuvir across 30 countries has shown that current prices of these medicines are variable and unaffordable globally. A fairer pricing framework is needed if countries are to increase investment to minimize the burden of hepatitis C.


**DNDi and pharmaceutical company to test new hepatitis C medicine**

**Barcelona** – The Drugs for Neglected Diseases initiative (DNDi) and the Egyptian pharmaceutical company Pharco Pharmaceuticals have signed agreements covering the clinical testing
and scale-up of a hepatitis C treatment regimen at a price of just under US$ 300. The announcement was made at the International Liver Congress 2016 in Spain. The regimen consists of a combination of ravidasvir – an NS5A inhibitor – and sofosbuvir. Phase III studies will be conducted in Malaysia and Thailand in patients with various levels of liver fibrosis, various genotypes of hepatitis C virus, and with and without HIV co-infection to compare the new regimen with the combination of sofosbuvir and daclatasvir, a current standard of care.

Disease updates

HIV and hepatitis C co-infection

Geneva – A WHO-commissioned study has found that an estimated 2.3 million people globally are co-infected with HIV and hepatitis C virus (HCV). More than half of these are people who inject drugs. HIV-infected people were found to be six times more likely than HIV-uninfected people to have HCV infection.

Globally, there are 37 million people infected with HIV and around 115 million people with chronic HCV infection. The study found that 27% of all HIV/HCV co-infections were in eastern Europe and central Asia, where injecting drug use is driving the co-infection epidemic. The sub-Saharan African region accounted for 19% of all cases due to high burdens of HIV.

This first global study of its kind was sponsored by WHO and conducted in collaboration with the London School of Hygiene & Tropical Medicine and the University of Bristol. It points to the need to improve HCV and HIV surveillance and integrated HIV/HCV services and to scale up preventive interventions and access to HIV and HCV treatment.

Diabetes: global action needed

Geneva – WHO has released its first global report on diabetes, which reveals that the number of people living with this disease has almost quadrupled since 1980. In 2014 an estimated 422 million adults were living with diabetes, most
of them living in developing countries. Diabetes caused 1.5 million deaths in 2012, of which 43% occurred before the age of 70 years. Diabetes has far-reaching health and socioeconomic impacts.

Good management of diabetes includes use of a small set of generic medicines, interventions to promote healthy lifestyles, patient education to facilitate self-care, and regular screening for early detection and treatment of complications. Insulin and oral hypoglycaemic agents are reported as available and affordable in only a minority of low-income countries. Global action is needed to halt the rise in diabetes and obesity, and to make affordable essential medicines available to all people living with diabetes.

► WHO News release, 6 April 2016.


Depression and anxiety: the investment case
The results of a new WHO-led study show that investing in treatment for depression and anxiety leads to fourfold returns in terms of better health and ability to work.

Depression and anxiety disorders cost the global economy US$ 1 trillion each year. Between 1990 and 2013, the number of people suffering from depression and/or anxiety increased by nearly 50%, from 416 million to 615 million or close to one tenth of the world’s population.

Governments spend on average 3% of their health budgets on mental health, ranging from less than 1% in low-income countries to 5% in high-income countries. Scaling up of mental health services is needed to achieve the Sustainable Development Goals target that calls for a reduction by one third, in the next 15 years, of the premature mortality from non-communicable diseases, including through promotion of mental health and well-being.


Multidrug-resistant tuberculosis: WHO recommends shorter regimen
Geneva –WHO has published new recommendations to speed up the detection and improve treatment outcomes for multidrug resistant tuberculosis (MDR-TB) through use of a novel rapid diagnostic test and a shorter, cheaper treatment regimen. At less than US$ 1 000 per patient, the new treatment regimen can be completed in 9–12 months, as opposed to 18–24 months for conventional regimens.

The shorter regimen is recommended for patients diagnosed with uncomplicated MDR-TB, for example those without resistance to fluoroquinolones and injectable second-line drugs, and those who have not yet been treated with second line drugs. A new diagnostic test – called MTBDRsl – gives results on resistance to second-line drugs in just 24-48 hours, down from the 3 months or longer required with other tests. This new test has the potential to support the appropriate use of the shortened treatment regimen and can thus help to accelerate the global MDR-TB response.

► WHO News release, 12 May 2016.
**Malaria: push for further progress**

Geneva – A WHO report released on the occasion of World Malaria Day shows that the goal to eliminate malaria from at least 35 countries by 2030, adopted a year ago by the World Health Assembly, is ambitious but achievable. Many countries are well on their way towards malaria elimination, and malaria mortality rates have declined by 60% globally since the year 2000. However, nearly half of the world’s population remain at risk of malaria, and there is an urgent need for greater investment in high transmission settings, particularly in Africa.

With growing mosquito resistance to insecticides and parasite resistance to antimalarials, new technologies need to be developed. As countries approach elimination, the ability to detect every infection also becomes increasingly important. Further progress in the fight against malaria will require strong leadership by governments of affected countries and an increase in global and domestic funding from currently $2.5 billion to about $8.7 billion annually by 2030. (1)

Two UNITAID reports published ahead of 2016 World Malaria Day foresee a rising demand for malaria diagnostics and treatment through 2018, despite recent sharp declines in malaria prevalence worldwide. Over 400 million treatments and a vast scale-up in the market for malaria rapid diagnostic tests are needed over the next three years to meet global targets for eliminating malaria. (2)

(2) UNITAID Press release, 21 April 2016.
UNITAID. Global Malaria Diagnostic and Artemisinin Treatment Commodities Demand Forecast: 2015-2018.
UNITAID. Malaria Diagnostics Technology and Market Landscape: 3rd Edition.

**Zika: WHO identifies research and development priorities**

Geneva – International experts convened by WHO have agreed on the research and development (R&D) priorities to protect pregnant women and their infants from the consequences of Zika virus infection. Products to be prioritized include multiplex tests for Zika and other flaviviruses such as dengue and chikungunya in addition to more traditional tests, inactivated Zika vaccines for women of childbearing age, and innovative vector control tools that reduce the mosquito population.

A number of such products are at an early stage of development. WHO will propose target product profiles for vaccines and diagnostics for public consultation. The R&D community has responded vigorously to WHO’s call for applications under the WHO Emergency Use, Assessment and Listing (EUAL) procedure. A major advance compared to the Ebola product R&D response of 2014–2015 is the speed with which data and experiences are being shared.

► WHO Note for the media, 9 March 2016.

**Ebola: no longer a public health emergency**

Geneva – The 9th meeting of the International Health Regulations (IHR) Emergency Committee has stated that the Ebola situation in West Africa no longer constitutes a Public Health Emergency of International Concern (PHEIC). The WHO Director-General has terminated the PHEIC in accordance with the International Health Regulations (2005) as well as the Temporary Recommendations that she had issued in relation to this event. The crucial need was emphasized for continued international donor and technical support to prevent, detect
and respond rapidly to any new Ebola outbreak in West Africa. (1)
In early June WHO declared the end of Ebola virus transmission in the Republic of Guinea (2) and in Liberia (3), as 42 days had passed from the second negative test of the last person with confirmed infection.

► (1) WHO Statement, 29 March 2016.
  (2) WHO AFRO News release, 1st June 2016.
  (3) WHO AFRO News release, 9 June 2016.

Vaccination

Recent gains and remaining gaps
Geneva – During World Immunization Week 2016, held on 24-30 April, WHO has highlighted recent gains in immunization coverage – with polio having eliminated in one country, tetanus in three, and rubella in one geographical region in 2015 – and has outlined further steps that countries can take to meet global vaccination targets by 2020 as defined in the Global Vaccine Action Plan. Immunization averts 2–3 million deaths annually. However, an additional 1.5 million deaths could be averted if global vaccination coverage improves.

Quality and use of data have been identified as factors that can help improve vaccine coverage. In accordance with a 2015 World Health Assembly resolution WHO has collected 1 600 vaccine price reports in what is today the largest international vaccine price database. Prices paid for vaccines represent a large share of countries’ immunization budgets, and cost can represent a barrier preventing countries from introducing new vaccines.

  WHO. V3P vaccine price database.

Controlled substances

A public health approach to the world drug problem
New York – At the United Nations General Assembly Special Session on the World Drug Problem held on 19-21 April in New York, WHO highlighted the public health dimensions of this issue. Psychoactive drug use causes more than 400 000 deaths each year and contributes significantly to epidemics of HIV, viral hepatitis and tuberculosis in all regions of the world. National drug policies often focus on law enforcement, with little attention given to prevention, treatment and harm reduction or access to controlled medicines. It is estimated that 83% of the world’s population live in countries with low or non-existent access to controlled medicines for the management of moderate to severe pain. (1)
WHO’s role in promoting a public health-oriented approach to addressing the world drug problem was also discussed by the WHO Executive Board and brought to the attention of the Sixty-ninth World Health Assembly. (2)

  (2) WHO Essential Medicines and Health Policies News, 1 March 2016.

WHO matters

Sixty-ninth World Health Assembly: setting the course for global public health
Geneva – Some 3 500 delegates from WHO’s 194 Member States attended the Sixty-ninth World Health Assembly, held on 23–28 May 2016. In her opening speech, the WHO Director-General
emphasized that universal health coverage will be key to achieving health-related targets of the sustainable development agenda.

The Assembly took a number of decisions related to medical products. It adopted global health sector strategies on HIV, viral hepatitis and sexually transmitted infections for the period 2016–2021, aiming to scale up treatment, use of diagnostics and prevention measures in line with the targets laid down in the Sustainable Development Goals. Delegates further agreed on a range of measures to ensure access to needed medicines and vaccines, to address global shortages (see also page 180), and to identify gaps in health research and development, especially for diseases that disproportionately affect developing countries and attract little investment.

Resolutions were approved on the new WHO health emergencies programme, the International Health Regulations, resilient integrated health services, the Sustainable Development Goals, WHO’s engagement with non-state actors, and a number of other issues.

► WHO News release, 28 May 2016.

New WHO medicines quality guidelines published
Geneva – WHO has published the 50th meeting report of its Expert Committee on Specifications for Pharmaceutical Preparations. The ten annexed guidelines include five new texts on such important issues as good data management practices, good pharmacopoeial practices, conducting medicines quality surveys, and provision by health professionals of children-specific medicines that are not available as authorized products. Revised guidelines were adopted on good manufacturing practices for biologicals (following their adoption by the Expert Committee on Biological Standards a day earlier), good trade and distribution practices for starting materials, and three other topics.

► WHO Essential medicines and health products. WHO Expert Committee on specifications for pharmaceutical preparations (Fiftieth report) [web page].

WHO announces Phase 7 of its external assessment scheme for quality control laboratories
Geneva – WHO has announced Phase 7 of its External Quality Assurance Assessment Scheme (EQAAS). The Scheme was established by WHO in 2000 at the request of the Global Fund as a mechanism to maximize health benefits achieved on grant investments in pharmaceuticals and laboratory supplies. The EQAAS has proven to be a major asset to WHO Member States. More than 60 laboratories across WHO’s six regions have participated in past studies. Participation in comparative external assessment studies is mandatory according to WHO’s good practices for pharmaceutical quality control laboratories and for ISO 17025 accreditation.

The WHO EQAAS is at present the only global, independent scheme to measure laboratories’ QC testing capabilities. WHO is pleased to be able once more to offer preferential fees far below cost for participants from low- and middle-income countries. For more information and expression of interest to participate, please contact WHO at EQAAS@who.int.

► Information about EQAAS:
WHO Essential medicines and health products. External quality assurance assessment scheme (EQAAS) [web page].
**Primaquine invited for prequalification**

Geneva – The WHO Prequalification Team has published its 10th Invitation for Expression of Interest (EOI) for prequalification of active pharmaceutical ingredients (API) and its 13th EOI for antimalarial medicines. The two revised EOIs newly include primaquine API and tablet formulations.

► **10th Invitation to manufacturers of Active Pharmaceutical Ingredients (API) to submit an Expression of Interest (EOI) for API evaluation to the WHO Prequalification Team: medicines. 27 April 2016.**

► **13th Invitation to manufacturers of antimalarial medicines to submit an Expression of Interest (EOI) for product evaluation to the WHO Prequalification Team - Medicines (April 2016).**

**Prequalification of vector control products**

Geneva – WHO has launched a new temporary website for the prequalification of vector control products. Review functions for these products, previously carried out by the Control of Neglected Tropical Diseases department, have been transferred to the WHO Prequalification Team (PQT). This reflects part of WHO’s evolving approach to supporting the development, evaluation and adoption of new vector control products and tools.

PQT’s quality assurance processes, together with its close engagement with regulatory authorities globally, build on WHO’s work to ensure that vector control products and pesticidal active ingredients (for public health purposes) are effective, safe, and meet stringent quality and manufacturing standards. Key steps of the prequalification process include assessment of product dossiers, inspection of manufacturing sites, and supporting quality control testing of products. Finally, products and manufacturing sites that meet prequalification requirements are added to (a) the WHO list of vector control products or (b) the WHO list of manufacturing sites for public health pesticidal active ingredients, respectively.

Current vector control interventions face serious challenges, including increasing insecticide resistance, rapidly expanding arboviral diseases and the impact of climate change on vector distributions. To respond to these challenges, there is an urgent demand for innovative vector control products and the development of new tools and approaches.

► **WHO Prequalification Team: vector control products** (WHO PQ update, 7 June 2016).
Upcoming events

17th ICDRA

Registration is now open for the 17th International Conference of Drug Regulatory Authorities (ICDRA), which will be held at the International Convention Centre (ICC) in Cape Town, South Africa, on 29 November–2 December 2016. A pre-ICDRA conference event titled “Patients are Waiting: How Regulators Collectively Make a Difference” will be convened on 27–28 November 2016 at the same venue.

The 17th ICDRA will facilitate focused discussions on medicines regulatory harmonization, strengthening of regulatory systems, regulatory preparedness around public health emergencies, collaboration and harmonization of medical device regulation, good regulatory practices and global convergence of standards (see page 173 for more information).

Registration for the pre-ICDRA conference event is open to delegates from medicines regulatory authorities and other interested parties such as industry, civil society, scientific institutions and non-governmental organizations. A registration fee is applicable to delegates other than medical products regulators. Registration for the 17th ICDRA is open exclusively to delegates from medicines regulatory authorities and is free of charge. The closing date for registrations is 31 August 2016. Early registration is encouraged.

► 17th ICDRA website, www.icdra.co.za

International Conference of Drug Regulatory Authorities (ICDRA)

The 17th ICDRA will take place in Cape Town, South Africa on 27 November – 2 December 2016

Register now: www.icdra.co.za
Closing date for registrations: 31 August 2016
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**

Revision of Chapter 2.6, Non-aqueous titration

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.646, May 2016). The working document with line numbers and tracked changes is available for comment at [www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/). Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidt@who.int.

*Note from the Secretariat.* As part of the activities to update *The International Pharmacopoeia*, mercury salts and other toxic reagents shall be replaced in order to reduce the risk to analysts and the environment. In the past, the addition of mercuric acetate has been necessary to permit the titration of halide salts of weak bases. These titrations can now be replaced by alternative procedures, notably the direct titration of the halide salts of weak bases with perchloric acid in anhydrous acetic acid or the titration of the halide salts of bases in alcoholic media with sodium hydroxide. As a first step in phasing out mercury-based methods, it is proposed to revise chapter 2.6. Non-aqueous titration. The monographs which currently prescribe the use of mercuric acetate for titrations will be gradually revised using the new recommended procedures Method A(i) and A(ii).

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

2.6. Non-aqueous titration

Acids and bases have long been defined as substances that, when dissolved in water, furnish hydrogen and hydroxyl ions, respectively. This definition, introduced by Arrhenius, fails to recognize the fact that properties characteristic of acids or bases may also be developed in other solvents. A more generalized definition is that of Brönsted, who defined an acid as a proton donor, and a base as a proton acceptor. Even broader is the definition of Lewis, who defined an acid as any material that will accept an electron pair, a base as any material that will donate an electron pair, and neutralization as the formation of a coordination bond between an acid and a base.

The apparent strength of an acid or base is determined by the extent of its reaction with a solvent. In aqueous solution all strong acids appear equally strong because they react with the solvent to undergo almost complete conversion to hydronium ion (H$_3$O$^+$) and the acid anion. In a weakly protophilic solvent such as acetic acid, the extent of formation of the acetonium ion (CH$_3$COOH$_2^+$) due to the addition of a proton provides a more sensitive differentiation of
the strength of acids and shows that the order of decreasing strength for acids is perchloric, hydrobromic, sulfuric, hydrochloric and nitric.

Acetic acid reacts incompletely with water to form hydronium ion and is therefore a weak acid. In contrast, it dissolves in a base such as ethylenediamine and reacts so completely with the solvent that it behaves as a strong acid.

This so-called levelling effect is also observed for bases. In sulfuric acid almost all bases appear to be of the same strength. As the acid properties of the solvent decrease in the series sulfuric acid, acetic acid, phenol, water, pyridine and butylamine, bases dissolved in them become progressively weaker and the differences between bases are accentuated. In order of decreasing strength, strong bases of value for non-aqueous titrations are potassium methoxide, sodium methoxide, lithium methoxide and tetrabutylammonium hydroxide.

Many water-insoluble compounds acquire enhanced acidic or basic properties when dissolved in organic solvents. Thus the choice of the appropriate medium and titrant permits the determination of a variety of such materials by non-aqueous titration. Further, depending upon which part of a compound is physiologically active, it is often possible to titrate that part by proper selection of solvent and titrant. The types of compounds, in a non-aqueous medium, that may be titrated as acids, by usually lithium methoxide or tetrabutyl ammonium hydroxide, include acid halides, acid anhydrides, carboxylic acids, amino acids, enols such as barbiturates and xanthonines, imides, phenols, pyrroles and sulfonamides. The types of compounds, in a non-aqueous medium, that may be titrated as bases, by perchloric acid, include amines, nitrogen-containing heterocyclic compounds, quaternary ammonium compounds, alkali salts of organic acids, alkali salts of inorganic acids and some salts of amines. Many halide salts of weak bases and some quaternary ammonium compounds may be directly titrated in acetic anhydride using, preferably, potentiometric end-point detection or an indicator such as malachite green or crystal violet.

In the titration of a basic compound amphiprotic solvents which have both protophilic and protogenic properties (e.g. acetic acid and the alcohols), which dissociate to a slight extent, are used as the medium. When acetic acid or acetic anhydride (halide salts of weak bases and quaternary ammonium compounds) is the medium, a volumetric solution of perchloric acid in glacial acetic acid may be used. When ethanol is used as the medium for halide salts of weak bases the titrant is a volumetric solution of sodium hydroxide. In the titration of an acidic compound a volumetric solution of lithium methoxide in a methanol-toluene solvent is often used. For many applications it is convenient to use a solution of tetrabutylammonium hydroxide in toluene; sodium methoxide, formerly in wide use, may often give rise to troublesome gelatinous precipitates.

Because of interference by carbon dioxide, solvents for acidic compounds must be protected from excessive exposure to the atmosphere by a suitable cover or by an inert atmosphere during the titration. A blank determination should be carried out and the volume generally should not exceed 0.01 mL of a 0.1 mol/L titrant for each mL of solvent.

The end-point may be determined visually by colour change or preferentially by potentiometry. If the calomel reference electrode is used it is advantageous to replace the aqueous potassium chloride solution in the salt bridge with lithium perchlorate/acetic acid TS for titrations in acidic solvents, or potassium chloride in methanol for titrations in basic solvents. It should be recognized that certain indicators in common use (crystal violet, for example) undergo a series of colour changes and, in establishing a non-aqueous titration method for a particular use, care should be taken to ensure that the colour change specified as the end-point of the titration
corresponds to the maximum value of $\frac{dE}{dV}$ (where $E$ is the electromotive force and $V$ the volume of titrant) in a potentiometric titration of the substance under consideration.

When using titrants prepared with solvents that may have a relatively high coefficient of expansion, for example, glacial acetic acid, toluene, etc., care should be taken to compensate for differences in temperature that may exist between the time the titrant is used and that at which it was standardized.

**Recommended procedures**

**Method A (i) – for halide salts of organic bases**

Dissolve a quantity of the substance being examined to give an expected titration volume of between 70–90% of the burette volume, in 50 mL of dehydrated ethanol R and 5.0 mL of hydrochloric acid (0.01 mol/L) VS. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS. Read the volume added between the two points of inflexion.

**Method A (ii) – for bases, their salts and quaternary ammonium compounds**

Prepare a solution as specified in the monograph or dissolve the substance being examined in a suitable volume of medium (anhydrous acetic acid R1 or acetic anhydride R with or without the addition of formic acid R or dioxan R). The titration blank for the medium is to be established in a separate determination. When the end-point is determined visually by colour change, add 2–3 drops of crystal violet/acetic acid TS and titrate with perchloric acid of the specified concentration (mol/L) to the appropriate colour change of the indicator. When a different indicator is specified in the monograph this indicator should also be used for the neutralization of the medium and the standardization of the titrant.

When the equivalence point is determined potentiometrically the indicator is omitted and neutralization of the medium and standardization of the titrant are also carried out potentiometrically. A glass electrode and a saturated calomel cell (containing potassium chloride (350 g/L) TS) as reference electrode are used. The junction between the calomel electrode and the titration liquid should have a reasonably low electrical resistance and there should be a minimum of transfer of liquid from one side to the other. Serious instability may result unless the connections between the potentiometer and the electrode system are in accordance with the manufacturer’s instructions.

When the temperature ($t_2$) at which the titration is carried out differs from the temperature ($t_1$) at which the titrant was standardized, multiply the volume of the titrant required by $[1 + 0.001 (t_1 – t_2)]$ and calculate the result of the assay from the corrected volume.

**Method B (for acids)**

The titrant, solvent and (in the case where the end-point is determined visually) the indicator to be used for each substance, are specified in the monograph.

Protect the solution and titrant from carbon dioxide of the atmosphere throughout the determination. This may conveniently be done by replacing the air above the titration liquid with nitrogen.
Dissolve the substance being examined in a suitable volume of the solvent previously neutralized to the indicator, warming and cooling if necessary, or prepare a solution as specified in the monograph. Titrate to the appropriate colour change of the indicator. Carry out a blank determination and make any necessary corrections. The titrant is standardized using the same solvent and indicator as specified for the substance.

When the equivalence point is established potentiometrically the indicator is omitted and neutralization of the solution and standardization of the titrant are also carried out potentiometrically.

A glass electrode and a saturated calomel reference electrode in which the aqueous potassium chloride (350 g/L) TS has been replaced by a saturated solution of potassium chloride R in methanol R are used. The junction between the calomel electrode and the titration liquid should have a reasonably low electrical resistance and there should be a minimum of transfer of the liquid from one side to the other. Serious instability may result unless the connections between the potentiometer and the electrode system are made in accordance with the manufacturer’s instruction.
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 March 2016.

Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology before 1 September 2016. If no objections are received before this date, the new ATC codes and DDDs will be considered final and included in the January 2017 version of the ATC/DDD Index.

New ATC 5th level codes

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<td>tiopronin</td>
<td>0.8</td>
<td>g</td>
<td>O</td>
<td>G04BX16(4)</td>
</tr>
</tbody>
</table>

* Administration Route: O=oral; P=parenteral
1) Refers to ceftolozane
2) Course dose
3) ATC code changed from L04AC06, new code valid from January 2017
4) ATC code changed from R05CB12, new code valid from January 2017

### Changes of DDDs

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

* Administration Route: O=oral; P=parenteral
The following ATC codes, DDDs and alterations were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in October 2015. These are considered as final and will be included in the January 2017 version of the ATC/DDD Index.

**New ATC 5th level codes**

*Please note that the list does not include new ATC codes established as a result of ATC alterations.*

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>aceneuramic acid</td>
<td>M09AX05</td>
</tr>
<tr>
<td>alectinib</td>
<td>L01XE36</td>
</tr>
<tr>
<td>alirocumab</td>
<td>C10AX14</td>
</tr>
<tr>
<td>aminobenzoate potassium</td>
<td>D11AX23</td>
</tr>
<tr>
<td>arterolane and piperaquine</td>
<td>P01BX02</td>
</tr>
<tr>
<td>carvedilol and ivabradine</td>
<td>C07FX06</td>
</tr>
<tr>
<td>cobimetinib</td>
<td>L01XE38</td>
</tr>
<tr>
<td>daratumumab</td>
<td>L01XC24</td>
</tr>
<tr>
<td>deoxycholic acid</td>
<td>D11AX24</td>
</tr>
<tr>
<td>desfesoterodine</td>
<td>G04BD13</td>
</tr>
<tr>
<td>edoxaban</td>
<td>B01AF03</td>
</tr>
<tr>
<td>elbasvir and grazoprevir</td>
<td>J05AX68</td>
</tr>
<tr>
<td>elotuzumab</td>
<td>L01XC23</td>
</tr>
<tr>
<td>eluxadoline</td>
<td>A07DA06</td>
</tr>
<tr>
<td>empegfilgrastim</td>
<td>L03AA16</td>
</tr>
<tr>
<td>etelcalcetide</td>
<td>H05BX04</td>
</tr>
<tr>
<td>ferric maltol</td>
<td>B03AB10</td>
</tr>
<tr>
<td>fluoroethyl-L-tyrosine (18F)</td>
<td>V09IX10</td>
</tr>
<tr>
<td>follitropin delta</td>
<td>G03GA10</td>
</tr>
<tr>
<td>gallium (68Ga) endotroetide</td>
<td>V09IX09</td>
</tr>
<tr>
<td>inotuzumab ozogamicin</td>
<td>L01XC26</td>
</tr>
<tr>
<td>ixekizumab</td>
<td>L04AC13</td>
</tr>
<tr>
<td>landiolol</td>
<td>C07AB14</td>
</tr>
<tr>
<td>metoprolol and ivabradine</td>
<td>C07FX05</td>
</tr>
<tr>
<td>metreleptin</td>
<td>A16AA07</td>
</tr>
<tr>
<td>mogamulizumab</td>
<td>L01XC25</td>
</tr>
<tr>
<td>osimertinib</td>
<td>L01XE35</td>
</tr>
<tr>
<td>phenylephrine and ketorolac</td>
<td>S01FB51</td>
</tr>
<tr>
<td>rociletinib</td>
<td>L01XE37</td>
</tr>
<tr>
<td>safinamide</td>
<td>N04BD03</td>
</tr>
<tr>
<td>salbutamol and beclometasone</td>
<td>R03AK13</td>
</tr>
<tr>
<td>talimogene laherparepvec</td>
<td>L01X51</td>
</tr>
<tr>
<td>tiazotic acid</td>
<td>C01EB23</td>
</tr>
<tr>
<td>tramadol and dexketoprofen</td>
<td>N02AJ14</td>
</tr>
<tr>
<td>trientine</td>
<td>A16AX12</td>
</tr>
</tbody>
</table>
New ATC level codes (other than 5th levels)

<table>
<thead>
<tr>
<th>ATC level name</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blocking agents, other combinations</td>
<td>C07FX</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 receptor (GLP-1) analogues</td>
<td>A10BJ</td>
</tr>
<tr>
<td>Opioids in combination with non-opioid analgesics</td>
<td>N02AJ</td>
</tr>
<tr>
<td>Sodium-glucose co-transporter 2 (SGLT2) inhibitors</td>
<td>A10BK</td>
</tr>
</tbody>
</table>

Change of ATC codes

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>Previous ATC code</th>
<th>New ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>albiglutide</td>
<td>A10BX13</td>
<td>A10BJ04</td>
</tr>
<tr>
<td>canagliflozin</td>
<td>A10BX11</td>
<td>A10BK01</td>
</tr>
<tr>
<td>dapagliflozin</td>
<td>A10BX09</td>
<td>A10BK02</td>
</tr>
<tr>
<td>dulaglutide</td>
<td>A10BX14</td>
<td>A10BJ05</td>
</tr>
<tr>
<td>empagliflozin</td>
<td>A10BX12</td>
<td>A10BK03</td>
</tr>
<tr>
<td>exenatide</td>
<td>A10BX04</td>
<td>A10BJ01</td>
</tr>
<tr>
<td>liraglutide</td>
<td>A10BX07</td>
<td>A10BJ02</td>
</tr>
<tr>
<td>lixisenatide</td>
<td>A10BX10</td>
<td>A10BJ03</td>
</tr>
<tr>
<td>mepolizumab</td>
<td>L04AC06</td>
<td>R03DX09</td>
</tr>
<tr>
<td>methotrexate</td>
<td>L01BA01</td>
<td>L04AX03</td>
</tr>
<tr>
<td>nonacog alfa</td>
<td>B02BD09</td>
<td>B02BD04</td>
</tr>
<tr>
<td>tiopronin</td>
<td>R05CB12</td>
<td>G04BX16</td>
</tr>
<tr>
<td>trenonacog alfa</td>
<td>B02BD12</td>
<td>B02BD04</td>
</tr>
</tbody>
</table>

1) Splitting of ATC code. Only the classification of pre-filled syringes of methotrexate for use in non-cancer indications is changed. These products will be moved to the existing ATC code for oral administered product of methotrexate. Parenteral preparations used for treatment of cancer will remain in L01BA01.

2) Existing ATC code B02BD04 coagulation factor IX

Change of ATC level names

<table>
<thead>
<tr>
<th>Previous</th>
<th>New</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>atenolol and other antihypertensives</td>
<td>atenolol and nifedipine</td>
<td>C07FB03</td>
</tr>
<tr>
<td>Beta blocking agents and other antihypertensives</td>
<td>Beta blocking agents, other combinations</td>
<td>C07F</td>
</tr>
<tr>
<td>Beta blocking agents, selective, and other antihypertensives</td>
<td>Beta blocking agents and calcium channel blockers</td>
<td>C07FB</td>
</tr>
<tr>
<td>bisoprolol and other antihypertensives</td>
<td>bisoprolol and amlodipine</td>
<td>C07FB07</td>
</tr>
<tr>
<td>nebivolol and other antihypertensives</td>
<td>nebivolol and amlodipine</td>
<td>C07FB12</td>
</tr>
<tr>
<td>oxycodone, combination</td>
<td>oxycodone and naloxone</td>
<td>N02AA55</td>
</tr>
</tbody>
</table>
### Change of ATC code and/or ATC level name based on new ATC 4th levels established

<table>
<thead>
<tr>
<th>Previous ATC code and level name</th>
<th>New ATC code and/or level name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C07FA</strong> Beta blocking agents, non-selective, and other antihypertensives</td>
<td><strong>C07FX</strong> Beta blocking agents, other combinations</td>
</tr>
<tr>
<td><strong>C07FA05</strong> propranolol and other antihypertensives</td>
<td><strong>C07FX01</strong> propranolol and other combinations</td>
</tr>
<tr>
<td><strong>C07AA57</strong> sotalol, combinations</td>
<td><strong>C07FX02</strong> sotalol and acetylsalicylic acid</td>
</tr>
<tr>
<td><strong>C07AB52</strong> metoprolol, combinations</td>
<td><strong>C07FX03</strong> metoprolol and acetylsalicylic acid</td>
</tr>
<tr>
<td><strong>C07FB02</strong> 1) metoprolol and other antihypertensives</td>
<td><strong>C07FB02</strong> metoprolol and felodipine 2) metoprolol and amiodipine</td>
</tr>
<tr>
<td><strong>C07AB57</strong> bisoprolol, combinations</td>
<td><strong>C07FX04</strong> bisoprolol and acetylsalicylic acid</td>
</tr>
<tr>
<td><strong>N02AA58</strong> 3) dihydrocodeine, combinations paracetamol, combinations excl. psycholeptics</td>
<td><strong>N02AJ01</strong> 4) dihydrocodeine and paracetamol</td>
</tr>
<tr>
<td><strong>N02BE51</strong> 3) dihydrocodeine, combinations acetylsalicylic acid, combinations excl. psycholeptics</td>
<td><strong>N02AJ02</strong> 4) dihydrocodeine and acetylsalicylic acid</td>
</tr>
<tr>
<td><strong>N02AA58</strong> 3) dihydrocodeine, combinations</td>
<td><strong>N02AJ03</strong> 4) dihydrocodeine and other non-opioid analgesics</td>
</tr>
<tr>
<td><strong>N02BA51</strong> 3) codeine, combinations excl. psycholeptics paracetamol, combinations excl. psycholeptics</td>
<td><strong>N02AJ04</strong> 4) codeine and paracetamol</td>
</tr>
<tr>
<td><strong>N02AA59</strong> 3) codeine, combinations excl. psycholeptics acetylsalicylic acid, combinations excl. psycholeptics</td>
<td><strong>N02AJ07</strong> 4) codeine and acetylsalicylic acid</td>
</tr>
<tr>
<td><strong>N02BA51</strong> 3) codeine, combinations excl. psycholeptics ibuprofen, combinations</td>
<td><strong>N02AJ08</strong> 4) codeine and ibuprofen</td>
</tr>
<tr>
<td><strong>M01AE51</strong> 3) codeine, combinations excl. psycholeptics</td>
<td><strong>N02AJ09</strong> 4) codeine and other non-opioid analgesics</td>
</tr>
<tr>
<td><strong>N02AA59</strong> 3) oxycodone, combinations paracetamol, combinations excl. psycholeptics</td>
<td><strong>N02AJ13</strong> tramadol and paracetamol</td>
</tr>
<tr>
<td><strong>N02BE51</strong> 3) oxycodone, combinations paracetamol, combinations excl. psycholeptics</td>
<td><strong>N02AJ17</strong> oxycodone and paracetamol</td>
</tr>
</tbody>
</table>

*Continued*
### Change of ATC code and/or ATC level name based on new ATC 4th levels established (continued)

<table>
<thead>
<tr>
<th>Previous ATC code and level name</th>
<th>New ATC code and/or level name</th>
</tr>
</thead>
<tbody>
<tr>
<td>N02AA55 3) oxycodone, combinations 3)</td>
<td>N02AJ18 4) oxycodone and acetylsalicylic acid</td>
</tr>
<tr>
<td>N02BA51 3) acetylsalicylic acid, combinations excl. psycholeptics</td>
<td></td>
</tr>
<tr>
<td>N02AA55 3) oxycodone, combinations 3)</td>
<td>N02AJ19 4) oxycodone and ibuprofen</td>
</tr>
</tbody>
</table>

1) Splitting of ATC code in connection with alterations in C07FX
2) Existing ATC code
3) Splitting of ATC codes according to contents of the different fixed combinations of opioids and other analgesics. The ATC codes in N02AA, N02BA51, N02BE51 and M01AE51 will be maintained for other combinations.
4) Combinations with opioids and other analgesics currently classified in the following ATC codes N02AA55, N02AA58, N02AA59 will be moved to the new ATC 4th level N02AJ. All the existing combination codes will be kept in N02AA since there may be other combinations without analgesics available (e.g. oxycodone and naloxone will remain in N02AA55). The ATC classification of all low dose combinations products of codeine or dihydrocodeine (<20 mg dose) currently classified in N02B or M01A will be altered to the new ATC codes in N02AJ.
5) Combinations of oxycodone and naloxone will be maintained in N02AA55.

### New DDDs

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>DDD</th>
<th>unit</th>
<th>Adm.R*</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>alirocumab</td>
<td>5.4</td>
<td>mg</td>
<td>P</td>
<td>C10AX14</td>
</tr>
<tr>
<td>apremilast</td>
<td>60</td>
<td>mg</td>
<td>O</td>
<td>L04AA32</td>
</tr>
<tr>
<td>ataluren</td>
<td>2.8</td>
<td>g</td>
<td>O</td>
<td>M09AX03</td>
</tr>
<tr>
<td>calcium acetate</td>
<td>6</td>
<td>g</td>
<td>O</td>
<td>V03AE07</td>
</tr>
<tr>
<td>cangrelor</td>
<td>50</td>
<td>mg</td>
<td>P</td>
<td>B01AC25</td>
</tr>
<tr>
<td>defibrotide</td>
<td>1.75</td>
<td>g</td>
<td>P</td>
<td>B01AX01</td>
</tr>
<tr>
<td>edoxaban</td>
<td>60</td>
<td>mg</td>
<td>O</td>
<td>B01AF03</td>
</tr>
<tr>
<td>elosulfase alfa</td>
<td>20</td>
<td>mg</td>
<td>P</td>
<td>A16AB12</td>
</tr>
<tr>
<td>ferric citrate</td>
<td>6</td>
<td>g</td>
<td>O</td>
<td>V03AE08</td>
</tr>
<tr>
<td>furazidin</td>
<td>0.3</td>
<td>g</td>
<td>O</td>
<td>J01XX03</td>
</tr>
<tr>
<td>iloperidone</td>
<td>18</td>
<td>mg</td>
<td>O</td>
<td>N05AX14</td>
</tr>
<tr>
<td>insulin degludec and li ragludite</td>
<td>40</td>
<td>U 1)</td>
<td>P</td>
<td>A10AE56</td>
</tr>
<tr>
<td>mifepristone, combinations</td>
<td>0.2</td>
<td>g 2)</td>
<td>O</td>
<td>G03XB51</td>
</tr>
<tr>
<td>naloxegol</td>
<td>25</td>
<td>mg</td>
<td>O</td>
<td>A06AH03</td>
</tr>
<tr>
<td>rifapentine</td>
<td>0.11</td>
<td>g</td>
<td>O</td>
<td>J04AB05</td>
</tr>
<tr>
<td>safinamide</td>
<td>75</td>
<td>mg</td>
<td>O</td>
<td>N04BD03</td>
</tr>
<tr>
<td>secukinumab</td>
<td>10</td>
<td>mg</td>
<td>P</td>
<td>L04AC10</td>
</tr>
<tr>
<td>tedizolid</td>
<td>0.2</td>
<td>g</td>
<td>O,P</td>
<td>J01XX11</td>
</tr>
</tbody>
</table>

* Administration Route: O=oral; P=parenteral
1) Refers to insulin degludec
2) Refers to mifepristone
**Change of DDD**

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>Previous DDD</th>
<th>New DDD</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DDD</td>
<td>Unit</td>
<td>Adm. R.*</td>
</tr>
<tr>
<td>ampicillin and enzyme inhibitor</td>
<td>2 g$^1$ P</td>
<td>6 g$^1$ P</td>
<td>J01CR01</td>
</tr>
<tr>
<td>Blood coagulation factors</td>
<td>2) Deleted</td>
<td></td>
<td>B02BD</td>
</tr>
<tr>
<td>mifepristone</td>
<td>0.6 g O</td>
<td>0.2 g O</td>
<td>G03XB01</td>
</tr>
</tbody>
</table>

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

1) Refers to ampicillin

2) DDDs for the various blood coagulation factors in all ATC 5th level codes in B02BD are deleted. No new DDDs will be established in B02BD Blood coagulation factors.

WHO Collaborating Centre
Oslo, May 2016