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CHMP Committee for Medicinal Products for Human Use (EMA)
EMA European Medicines Agency (www.ema.europa.eu)
EU European Union
FDA U.S. Food and Drug Administration (www.fda.gov)
Health Canada Federal department responsible for health product regulation in Canada (www.hc-sc.gc.ca)
MHRA Medicines and Healthcare Products Regulatory Agency, United Kingdom (www.mhra.gov.uk)
Medsafe New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz)
PRAC Pharmacovigilance Risk Assessment Committee (EMA)
PMDA Pharmaceutical and Medical Devices Agency, Japan (www.pmda.go.jp/english/index.html)
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.
WHO Prequalification

Building quality-assured manufacturing capacity in Nigeria

As a fast growing economy and large provider of goods and services to countries in the region, Nigeria is poised to expand its pharmaceutical production to achieve self-sufficiency in essential medicines and compete on regional and global markets. To this end, government health authorities and local manufacturers requested WHO support and technical assistance to prequalify several locally produced medicines, as a way to fast-track the building of local capacity to manufacture medicines according to international quality standards. An integral part of the process is the strengthening of national regulatory capacity to enforce these standards on an ongoing basis.

The Nigerian quest
While no medicines manufacturer in West Africa has so far achieved prequalification of a pharmaceutical product by the World Health Organization (WHO), Nigeria is attempting to change the status quo. A number of companies belonging to the Pharmaceutical Manufacturers Group of the Manufacturers Association of Nigeria (PMG-MAN) are working to reach a manufacturing quality standard that will enable them to have some of their products WHO-prequalified and apply for international medicines tenders.

The project has been supported by the Nigerian government and by the National Agency for Food and Drug Administration (NAFDAC). WHO was approached to provide technical assistance to both manufacturers and regulators especially in the areas of good manufacturing practice and dossier submissions in line with WHO and international standards.

Role of WHO
The WHO prequalification programme aims to ensure that medicines for priority diseases meet global standards of quality, safety and efficacy. By evaluating needed pharmaceutical products – including those produced in countries with limited regulatory capacity – the WHO prequalification team (WHO/PQT) provides a basis for national and international procurers to make cost-effective choices among finished products of assured quality.

WHO/PQT has increasingly engaged in activities that go beyond dossier assessment and site inspections. The team is training national regulators, providing guidance to manufacturers, facilitating registration in countries and supporting post-procurement quality control. The experts who advise manufacturers in preparing prequalification submissions work independently of the prequalification dossier assessment and inspection groups. The main objective of these activities is to disseminate sound knowledge and practices and to ensure that all the actors work together according
to the same international quality standards.

From the WHO perspective, the Nigerian project is in line with these aims. Given the importance of Nigeria in its geo-economic region, it is hoped that increased production of quality medicines in the country will also lead to better quality medicines in West Africa as a whole.

**Snapshot of Nigeria’s pharmaceutical landscape**

Nigeria is a natural candidate for the local capacity strengthening offered by WHO/PQT. The country’s pharmaceutical industry is vibrant and expanding, with over 100 pharmaceutical manufacturers and a mostly local ownership organized under the umbrella of the Pharmaceutical Manufacturers Group of the Manufacturers Association of Nigeria (PMG-MAN). Nigeria accounts for approximately 60% of the pharmaceutical production in the Economic Community of West African States (ECOWAS) by volume (1). Production is geared mostly towards essential medicines, including antimalarials and HIV medicines.

On the other hand, drug manufacturers in Nigeria face a number of constraints. These include a weak financial base, high production costs as a result of the high cost of imported pharmaceutical ingredients and machinery, infrastructural problems, outdated technology and weak distribution systems. In addition, as there are no contract research organizations in West Africa proven to work in line with international standards, manufacturers need to rely on expertise from Europe and Asia when they require bioequivalence studies or specific laboratory testing. Due to these factors, the country imports about 70% of its medicines, mainly from Asia, Europe and the Americas.

In terms of the regulatory environment, the National Agency for Food and Drug Administration and Control (NAFDAC) has in recent years enacted numerous enforcement activities to combat substandard and counterfeit medicines. It has also consistently worked with WHO to strengthen its quality control and post-marketing monitoring of pharmaceuticals. But challenges persist, which are largely related to insufficient capacity to ensure full regulatory functions in line with international standards, including speedy registration of medicines.

Despite these challenges, the country’s pharmaceutical sector is one of the strongest in Africa in terms of size, range of products manufactured and potential to meet and sustain international pharmaceutical quality standards.

**The project**

**Selection of manufacturers**

In 2011 NAFDAC and WHO/PQT came to an agreement on the principles of the project and, in collaboration with PMG-MAN, selected eight manufacturers that had expressed commitment to invest in quality improvements and that were deemed technically ready to embark on a programme to align their manufacturing operations with international quality standards. WHO/PQT arranged for external experts to verify the production standards at the manufacturing sites and to assess product data and documentation.

**Capacity-building**

Based on the results of the assessments by the external experts, WHO/PQT initiated an intensive capacity-building programme for Nigerian manufacturers.
and regulators. Since 2012, several training sessions on good manufacturing practices, combined with site visits at participating companies, have been co-organized by WHO/PQT and NAFDAC. In parallel, WHO-appointed experts have advised the companies on specific quality issues related to various medicines. In response to observations raised during the audits and document reviews, the companies implemented a series of corrective actions. They upgraded their equipment, improved manufacturing processes, and established professional procedures to build documentation for pharmaceutical ingredients and finished products. These corrective actions exceed currently applicable regulatory requirements in Nigeria. Implementation is monitored by NAFDAC professionals, who report on progress to WHO. The process is ongoing, with a current focus on the development of technically sound product dossiers.

WHO/PQT also works with the participating manufacturers to identify all their medicinal products eligible for prequalification. This will facilitate progress towards GMP-compliant production of additional medicines of interest for international organizations. For example, interest may come from UN Commission for Lifesaving Commodities for Women and Children (UNCoLSC), given that a large portion of the medicines needed in the West African region are reproductive health and paediatric products.

Regulatory and in-country support
On the regulatory side, NAFDAC has proved to be a strong partner in capacity-building efforts. The authority has upgraded its laboratories, recruited more specialized staff and has established new departments, such as the Clinical Trial/Pharmacovigilance and Post Marketing Surveillance and Drug Evaluation and Research Directorates. NAFDAC professionals also participate actively in trainings organized for local industry. The close support by the WHO Country Office has also been an asset to the project. The process has opened doors for Nigerian stakeholders and international organizations to work together more closely.

Pre-submission audits
The WHO prequalification team normally plans its inspections on a risk-basis once companies have submitted a prequalification dossiers. To enable applicants to work on product dossiers and good manufacturing practice (GMP) in parallel, the new concept of pre-submission GMP audits was piloted in Nigeria. An inspection can be scheduled before a dossier has been submitted, provided that the expert advisors and NAFDAC notify WHO/PQT that the manufacturer has achieved – in principle – compliance with WHO GMP. Prequalification inspectors then verify the status of general GMP compliance while completion of a prequalification dossier is still ongoing.

Successful audits represent a milestone in the progress towards prequalification, and the outcomes are considered by organizations looking for companies that manufacture needed health products in line with international GMP. A series of pre-audits was organized in 2013 and 2014 at Nigerian manufacturing sites in close co-operation with NAFDAC, whose regulatory inspectors played an active role in verifying the corrective actions adopted after the audit and drafting parts of the inspection reports.
Funding
The Nigerian Ministry of Health has invested considerably into the project. In addition, advocacy is on-going for a special intervention fund from the development banks in Nigeria, ECOWAS and the African Development Bank (AfDB).

WHO’s participation in the project has largely depended on financial backing from UNITAID, which was used to support technical assistance, transfer of knowledge, capacity building, audits and inspections and human resources.

From the manufacturers’ side, information from PMG-MAN indicates that the companies participating in the project have invested a cumulative amount exceeding USD 400 million over the last four years.

Achievements

GMP compliance
The pre-submission audits led to a landmark success being achieved in April 2014, when Swiss Pharma Nigeria Limited (Swipha) was confirmed to be operating at an acceptable level of compliance with WHO GMP guidelines for the manufacture of oral solid dosage forms (2). Swipha was the first pharmaceutical manufacturer in Sub-Saharan West Africa to pass a GMP inspection by WHO/PQT after implementing successful corrective and preventative action (CAPA). Three other companies participating in the project - Evans Medical Plc, May & Baker Nigeria Plc and CHI Pharmaceuticals Ltd – reached this standard in November 2014, after successfully implementing corrective and preventive action (CAPA) identified during WHO pre-submission audits in May 2014 (3).

Prequalification dossiers
One Nigerian company has submitted a prequalification dossier to WHO and this has been accepted for screening. Another submission is expected before the end of the year, with more to follow in the near future. The choice of medicines includes antimalarials, antiretrovirals, zinc sulphate and antibiotics.

Outlook and impact

Tenders
The achievements made by participating manufacturers open up opportunities for international tenders, where compliance with stringent GMP is a minimum requirement for any pharmaceutical product. Additional requirements apply to key categories such as antiretrovirals, anti-TB products and antimalarials. In these categories, compliance with stringent GMP enables manufacturers to apply for review of relevant products by the Expert Review Panel (ERP). Products that have received a positive ERP opinion can then compete in international tenders in situations where no or only one WHO-prequalified or stringently authorized competitor product is available on the market (4).

It is hoped that African ministries of health, regional initiatives and international procurers will consider WHO GMP-compliant African manufacturers in tenders for purchase of medicines in the region. This would support quality-assured local production, and would signal recognition of the cost that quality assurance entails for manufacturers.

Raising the bar for medicines quality
Feedback from PMG-MAN suggests that the project is beginning to yield wider benefits. The understanding of world class manufacturing practices in
Nigeria has improved. As a result, the perception of the importance of quality in pharmaceutical manufacturing is gradually shifting. Other Nigerian companies do not want to be left behind and are also becoming interested in upgrading their production, with support from PMG-MAN, to achieve WHO prequalification of their products.

NAFDAC has benefitted through hands-on participation in prequalification inspections, assessments, training workshops and other capacity-building activities, with access to prequalification inspection and assessment reports.

Local regulatory oversight
Medicines regulation is essentially a public function that should be assured by the governments of countries where medicines are produced and used. NAFDAC’s active follow-up of individual manufacturers’ progress and verification of corrective actions has proved extremely valuable in working towards this goal. The process has strengthened communication between industry and regulators, with a common understanding of the quality issues at stake.

The cooperation with NAFDAC under this project marks the start of a new model whereby the local regulatory authority assumes responsibility for ensuring that WHO prequalification requirements continue to be met. This approach is of course dependent on objective evidence that the local regulatory authority can in fact conduct routine monitoring and maintenance to the required standards. The activities will therefore be coordinated with, and reported to, WHO/PQT. In addition, NAFDAC assessors will work closely with the WHO prequalification assessors to review product dossiers submitted by Nigerian companies in line with international standards.

Challenges
Further challenges lie ahead before the Nigerian pharmaceutical sector will be able to reach the level of quality production and autonomy to which it aspires. Most challenges are related to the need for further guidance in manufacturing practices, dossier development, bio-equivalence and supply chain management. To address these needs, the initial timeline for the project was extended.

Important also is the choice of products for prequalification, which must be well considered to ensure that it serves both quality and commercial objectives.

Other challenges are related to financing. Given the fact that WHO prequalification will not occur immediately, financial incentives may well be needed for the companies to continue to progress. And while WHO prequalification of a number of Nigerian-made products in the near future seems feasible and can enable companies to win international procurement tenders, further change is needed to ensure a sustainable supply of quality medicines in the region and to resolve supply management problems.

Conclusion
The close cooperation between Nigerian manufacturers, regulators and WHO starts to produce results. The general understanding of international regulatory standards has improved, and several companies are well on their way towards prequalification of their products.

As corrective measures and upgrades continue, Nigerian authorities and manufacturers will need to find ways to raise sufficient funds to put into place
sustainable structures and processes for production of quality-assured pharmaceuticals.

Spokespersons of NAFDAC and PMG-MAN have expressed satisfaction with progress made to date and remain firmly committed to enhancing the pharmaceutical sector to make it work both for public health and the pharmaceutical industry.

WHO will continue to advocate for greater support of this kind of cross-sectoral capacity-building. Ensuring that affordable, quality-assured medicines are within reach of all those who need them is a pillar of an effective health system and an area requiring greater attention from the international community.

References


2. WHO/PQT. First Nigerian manufacturer considered compliant with WHO GMP. Prequalification Update, 4 April 2014.


Pharmacopoeial standards

Global specifications: the example of capreomycin

Capreomycin is used to treat multi-drug-resistant tuberculosis, an increasing public health problem. The example of the new capreomycin monographs in The International Pharmacopoeia shows how international specifications can provide added value for WHO Member States, including countries with resource limitations.

Public quality control standards
Pharmacopoeial monographs can be used by manufacturers, regulators and other stakeholders for quality control of active pharmaceutical ingredients (APIs) and finished products against internationally recommended specifications. Pharmacopoeial requirements in countries form part of national legislation, defining the specifications which pharmaceutical products circulating on their market must fulfil.

The International Pharmacopoeia (1) was created to help promote harmonized and suitable quality control testing standards among WHO Member States. It aims to provide analytical tests that can be performed with the recommended equipment for first-stage and medium-sized pharmaceutical quality control laboratories (2) in all regions of the world, including remote areas.

Focus on ‘neglected monographs’
The International Pharmacopoeia focuses on essential medicines that are of public health importance in WHO Member States, and for which monographs are not available in other pharmacopoeias. An example of such a medicine is capreomycin, an aminoglycoside antibiotic discovered in 1960 and first registered in 1971. Today it is part of WHO-recommended regimens to treat multi-drug-resistant tuberculosis, an increasing public health threat in many parts of the world.

Capreomycin was removed from the British Pharmacopoeia in 2003 because of its low use in the UK. Although monographs for capreomycin are included in the United States Pharmacopeia (USP) as well as the Chinese and Indian Pharmacopoeias, WHO decided to develop a further public standard because it was felt that the available methods and specifications were not sufficient to fully characterize and standardize the quality of the substance.

Input from world experts
Experts from universities, WHO Collaborating Centres and national regulatory authorities collaborated to develop the monographs for capreomycin sulfate active substance and capreomycin injection through WHO’s defined step-wise process (3). The initial drafts underwent two public consultations, during which many valuable comments were received. The new monographs were published in the Third and Fourth Supplement of The International Pharmacopoeia respectively. Their advantages for users are outlined on the next page.
Capreomycin monographs: Added value for WHO Member States

Comprehensive description
Produced by fermentation, capreomycin is a mixture of several structurally related components and thus difficult to characterize. The International Pharmacopoeia is currently the only pharmacopoeia to give comprehensive information on structures, formulas, relative molecular weights and chemical names for all four major components (capreomycin IA, IB, IIA and IIB). This information facilitates the production and registration of products containing capreomycin.

Alternative options for identity test
Two alternative combinations of identity tests are provided, for users to choose the option that can be performed using the equipment that is available in the laboratory (see Table 1).

Table 1. Options for identity test

<table>
<thead>
<tr>
<th>Test</th>
<th>Option 1</th>
<th>Option 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>IR Spectrophotometry</td>
<td>■</td>
</tr>
<tr>
<td>B</td>
<td>Thin-layer chromatography</td>
<td>■</td>
</tr>
<tr>
<td>C</td>
<td>Absorption spectrum of solution in hydrochloric acid</td>
<td>■</td>
</tr>
<tr>
<td>D</td>
<td>Absorption spectrum of solution in sodium hydroxide</td>
<td>■</td>
</tr>
<tr>
<td>E</td>
<td>General identification test for sulfates</td>
<td>■</td>
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</tbody>
</table>

First-ever pharmacopoeial test for related substances
The impurities of capreomycin affect the safety of the finished product. The International Pharmacopoeia describes the first-ever pharmacopoeial related substances test for capreomycin and defines acceptable limits for impurities – not an easy task, as toxicity data for old medicines like capreomycin can be challenging to put together. The test uses a high performance liquid chromatography (HPLC) method, a widely used analytical technique (see Figure 1).

Quantification of content
Other pharmacopoeias propose a microbiological assay, where the content of capreomycin is measured through its inhibitory effect on susceptible microorganisms. The assay in The International Pharmacopoeia is based on the same HPLC method as the related substances test (Figure 1), enabling a direct calculation of the content in terms of mass. This saves time and resources as the laboratory can perform two tests with the same analytical system.

Easy-to-use reference standard
A solution of the reference substance with a defined concentration is needed to quantify capreomycin. Capreomycin absorbs water from the atmosphere. It may therefore be difficult to weigh the substance accurately on an analytical balance.

The European Directorate for the Quality of Medicines and Healthcare (EDQM) is responsible for the establishment and distribution of WHO's International Chemical Reference Substances. Given the importance of this project and the objective difficulty of weighing capreomycin in a laboratory, the EDQM is currently assessing the feasibility of lyophilizing the reference standard. If this is feasible, the use of the ICRS will become fairly simple i.e. just adding to the vial a predefined volume of solvent.

Quantification of capreomycin components and related substances by HPLC
The HPLC method separates the different related compounds in capreomycin sulfate according to their affinity to a lipophilic stationary phase. In the resulting chromatogram the content of each compound is proportionate to the area of the corresponding peak.

Related substances: The peak response areas for the impurities are compared with those of the major peaks for capreomycin IA, IB, IIA and IIB; Acceptance limits are:
- All impurities ≤ 2%
- Only one impurity between 1 and 2%
- Sum of all impurities: ≤ 7%

Assay: The content is calculated from comparing the four major peak areas of the test substance with those of the reference substance, which has a declared content of capreomycin IA, IB, IIA and IIB.

Figure 1. Typical chromatogram showing the separation of the four main components of capreomycin sulfate (7, 9, 12 and 13) and related substances. Source: Reference (5).
Supporting market entry of quality-assured products

*The International Pharmacopoeia* is aligned with the needs of the WHO prequalification programme, which assesses the quality of medicines for procurement by UN agencies and other buyers that have recognized the central importance of medicines quality not only in treating individual patients, but also in reducing the risk of resistance that could make a medicine ineffective for entire populations.

Capreomycin is invited for WHO prequalification. At the end of September 2014 the first API was prequalified, another was under assessment. The first capreomycin injection was prequalified in October 2014, with four other submissions under assessment (4). Appropriate specifications and suitable test methods will support manufacturers in achieving WHO prequalification for their products, resulting in additional quality-assured products on the global market.

Funding

In the past, the work on *The International Pharmacopoeia* used to be funded from WHO’s regular budget. This funding source has decreased to virtually zero in recent years. The activities are currently funded for the most part by UNITAID, whose financial contribution is gratefully acknowledged. In addition, WHO Member States provide in-kind contributions and support valued at a multiple of the programme’s operational budget. These contributions include activities by national quality control laboratories, national support to WHO collaborating centres, and – very importantly – time given by individual experts.

Conclusion

Quality control testing is a mainstay of pharmaceutical quality assurance in production and regulation. In providing well-designed, globally applicable specifications and test methods for widely used medicines free of charge, WHO fills a need in Member States. *The International Pharmacopoeia* is useful in development, production, registration and post-market surveillance in countries around the world, and thus helps to ensure that essential medicines used in WHO Member States meet the internationally accepted quality requirements that make them safe and effective.

References


4. WHO. List of all APIs and FPPs invited for prequalification, and number prequalified or currently under assessment per product, (25 September 2014). Available from apps.who.int/prequal - Information for applicants.

Medicines quality assurance
A harmonized self-assessment tool for procurement agencies

In the absence of stringent regulatory systems for medicines in many parts of the world, procurement agencies have an important role in ensuring the quality of pharmaceutical products that they buy for use in treatment programmes. During the recent update of WHO’s quality assurance guidance for procurement agencies, a harmonized tool was developed enabling procurement agencies to assess their compliance with the principles of this guidance.

Background
The WHO Model Quality Assurance System for Procurement Agencies (MQAS) (1) is a WHO guidance document developed at the request of the Global Fund to Fight AIDS, Tuberculosis and Malaria and adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 2006. In the years that followed, international organizations involved in medicines procurement incorporated the MQAS requirements into their quality assurance policies and phased in stringent, harmonized quality criteria for key product categories procured in large quantities and considered crucial for the success of treatment programmes.

In introducing harmonized quality requirements for priority medicines, an important element of the MQAS was its Appendix 6, the interagency product questionnaire. It was adopted as the common format for suppliers to submit data for needed medicines that were not yet available as stringently approved or WHO-prequalified products.

Beyond priority medicines
In August 2011 international organizations came together at a meeting convened by WHO and the Global Fund to discuss ways to assure the quality of all essential medicines being procured, including those not belonging to the key categories.

It was found that for these diverse products often purchased in small quantities, the MQAS did provide valid approaches for quality assurance in procurement. The different agencies had strong quality assurance capacities, and several of them had developed their own systems to implement the MQAS principles. However this resulted in diverging practices and requirements, with duplication of efforts. The need was

The assessment tool presented in this article was developed by an interagency working group comprised of following members: A.J. van Zyl (Consultant) – coordinator; S. Arsac-Janvier, International Committee of the Red Cross (ICRC); J.-M. Caudron, Quality Medicines for All (QUAMED); L. Chacksfield, Crown Agents; J. Daviaud, Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund); M. de Goeje, International Dispensary Association (IDA) Foundation; S. Hamel, United States Agency for International Development (USAID); N. Heltzer, Management Sciences for Health (MSH); S. IJland, IDA Foundation; P. Svarrer Jakobsen, United Nations Children’s Fund (UNICEF); E. Jambert, Médecins Sans Frontières (MSF); S. Logez, Global Fund; C. Macê, WHO Policy Access and Use (WHO/PAU); P. Marroquin Lerga, Global Drug Facility (GDF); C. Perrin, International Union Against Tuberculosis and Lung Disease (The Union); B. Runbeck, Partnership for Supply Chain Management (PFSCM); E. Seaver, USAID; M. Sesay, United Nations Office for Project Services (UNOPS); A. Seiter, World Bank; C. Werder, Global Fund.
Table 1. Standardized assessment of compliance with the six MQAS modules

<table>
<thead>
<tr>
<th>Module I</th>
<th>Module II</th>
<th>Module III</th>
<th>Module IV</th>
<th>Module V</th>
<th>Module VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>General requirements (33 items)</td>
<td>Pre-qualification (21 items)</td>
<td>Purchasing (10 items)</td>
<td>Receiving – sampling and testing – storage (7, including 1 critical)</td>
<td>Containers and labelling (6, including 1 critical)</td>
<td>Reassessment (1)</td>
</tr>
<tr>
<td>Organization and management (2 items)</td>
<td>Prequalification procedure (4, including 1 critical)</td>
<td>Monitoring of performance of prequalified manufacturers (2)</td>
<td>Quality control (6)</td>
<td>Dispatch (10)</td>
<td>Reassessment of manufacturers (3)</td>
</tr>
<tr>
<td>Personnel (3)</td>
<td>Expression of interest (2)</td>
<td>Inspections (7)</td>
<td>Storage (9, including 1 critical)</td>
<td>Transport and transit (7)</td>
<td>Reevaluation of products (5)</td>
</tr>
<tr>
<td>Quality systems (10, including 2 critical)</td>
<td>Product information, screening and evaluation (5)</td>
<td>Prequalification outcome (3)</td>
<td>Stock control (13)</td>
<td>Monitoring of contracted-out services (4)</td>
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<td>Documentation (9)</td>
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<tr>
<td>Counterfeit products (3, including 2 critical)</td>
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<td>Self-inspection (2)</td>
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<tr>
<td>Complaints (2)</td>
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<tr>
<td>Recalls (2 critical)</td>
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How it works: A total of 137 items are rated on a scale of 0–100%. Compliance is taken as an overall rating of at least 60% (“Medium level of implementation, e.g. procedures have been developed, but lack scope and depth”) across the 137 items. Depending on the context, a rating of less than 60% for a critical item can lead to the entire module being considered non-compliant.

identified for a harmonized tool to assess compliance with the MQAS.

Measuring compliance with WHO guidance principles
An informal, voluntary working group was established at the 2011 meeting and worked together over the next two years to propose a harmonized MQAS compliance self-assessment tool. The tool is based on the six modules of the MQAS, with percentage ratings allocated to a total of 137 items, including ten critical items (Table 1). At the same time, the group updated the MQAS guidance itself and complemented it with an aide-memoire for inspection of procurement agencies (2).

The full self-assessment tool developed by the working group, together with instructions and a model report format, is reproduced in Annex 1. It supplements the formal WHO guidance texts by providing a consistent yet flexible way to measure the implementation of the principles defined in the guidance.

This tool will enable procurement agencies to assess themselves, to communicate the outcomes in a standardized way, and to take targeted measures for improvement.

References

Annex 1: Self-assessment tool based on the WHO Model Quality Assurance system for procurement agencies (MQAS)

a) Instructions

For whom is this tool intended, and who can use it? The tool can be used by the Quality Manager in a procurement agency for self-assessment of the agency and to identify its level of compliance with the standards as recommended by WHO in the MQAS.

What does the tool contain? The tool contains statements relating to systems and procedures that should be in place in a procurement organization as a means to assess the quality of systems and medicines.

Level of implementation of a system:
- 0%  No compliance, or the system/procedure does not exist
- 20%  Very low level of compliance or implementation
- 40%  Low level of compliance or implementation
- 60%  Medium level of implementation (e.g. procedures have been developed, but lack scope and depth)
- 80%  A good level of compliance
- 100% Fully implemented and consistently complies with MQAS expectation

Steps in the procedure for assessment:
1. Inspect the individual requirements in each system of each Module.
2. Allocate the percentage to indicate the level of compliance (0–100%). In case the activity is not applicable to the PA, state N/A and do not allocate “0”.
3. Make additional notes on deficiencies in the space provided (if needed) in each section.
4. Calculate the percentage compliance in each Module (I – VI)
5. Reach a conclusion on the level of compliance of the site in each area.
6. For critical issues (marked as !), a score below 60% indicates failure of compliance with standards and may result in an outcome of “non-compliant”.
7. Prepare a report based on the findings and present it in the agreed format.

For each module the calculated level of compliance will fall within one of the three levels below:
- Level I: <60% (Not in compliance – unacceptable)
- Level II: 60% (Acceptable level of compliance)
- Level III: >80% (High level of compliance)
### b) Self-assessment tool

An Excel version of this tool is available on request from: druginfo@who.int.

<table>
<thead>
<tr>
<th>Number</th>
<th>System/Procedure (&quot;1&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MODULE I: Organization and management</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>An authorized organization chart indicates positions, names of responsible persons and reporting lines and is in line with the job descriptions.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>There are written job descriptions defining responsibilities, for all personnel – signed by each employee. The person responsible for prequalification and the person responsible for purchasing is independent of one another.</td>
<td></td>
</tr>
<tr>
<td><strong>Personnel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>There is a sufficient number of qualified, trained staff with the necessary experience and authority to carry out their duties for key activities (including prequalification, purchasing, storage, distribution).</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Relevant personnel have signed and follow an authorized written code of conduct, confidentiality agreements and declaration of interest. These are archived and accessible for verification to ensure that there is no adverse effect on the quality of service provided or on the integrity of pharmaceutical products.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Personnel are trained in accordance with a standard operating procedure (SOP) and training programme, and assessment records are maintained.</td>
<td></td>
</tr>
<tr>
<td><strong>Quality system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>The PA is authorized/licensed to perform the activities (e.g. distribution of pharmaceutical products) in accordance with national legislation.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Authorized procurement and release procedures for all administrative and technical operations performed are in place to ensure that approved pharmaceutical products are sourced only from approved suppliers and distributed by approved entities to persons or entities authorized to acquire such products.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Any delegated and contracted activities are documented in agreements or contracts, and are within the legal framework of the country. There is evidence that the contract accepter complies with the legal requirements and GDP.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>The contracts clearly define responsibilities of the parties. Contracts are signed and dated.</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Contract accepters are audited periodically and reports show evidence of findings and corrective actions being taken.</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Defined procedures are implemented where the distributor is using electronic systems. These systems and procedures are proven to be reliable and ensure traceability. Transactions are performed only by authorized persons or entities.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Safety procedures are in place and cover personnel, property, environmental protection and product integrity.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>There is a quality manual in place. The quality policy is implemented.</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>There is sufficient office space, and other storage space for retention of commodities, documentation, samples, stock, reports, files and other records.</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Computer system applications are appropriate for their intended use. (Including appropriate hardware and software with security systems access; virus protection; firewall; technical support; capacity and memory; maintenance and upgrading plan, and batch traceability). A back-up of electronic records is made and maintained to prevent any accidental data loss.</td>
<td></td>
</tr>
</tbody>
</table>

Continued
### Number System/procedure (*"!" = critical) Rating

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (*&quot;!&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>A comprehensive documented system exists covering policies, organizational structure(s), procedures, guidelines, norms, standards, manuals, records and related documents.</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Activities are documented in authorized SOPs (signed and dated). SOPs for all activities are in an appropriate format and cover at least but are not limited to. - How to write an SOP: - Product dossier evaluation; - Inspections; - Decision making process for products; - Purchasing; - Receiving; - Issuing and dispatch; - Deviations; - Change control; - Evaluating offers received; - Handling of complaints; - Handling recalls; - Regular reinspection; - Quality control - Handling counterfeit/substandard products; - Handling variations; - Evaluating offers received.</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Documents are designed, completed, reviewed, amended and distributed with care. Documents are reviewed regularly and kept up to date. Superseded documents are removed from use.</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>There is evidence that risk assessment is done to assess potential risks to the quality and integrity of products.</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>An SOP is followed to manage changes such as changes to SOPs and other documents, facilities etc.</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Procedures cover health and hygiene of personnel. These are implemented and followed.</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Records (electronic or hard copies, also for manual systems) are maintained for a defined period and ensure product traceability throughout the supply chain which cover products received and distributed. (From the manufacturer/ importer to the entity responsible for selling or supplying the product to the patient.) These are readily retrievable with no unauthorized changes, damage, deterioration and/or loss thereof.</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Records for receiving of products contain at least the date; name of the product; batch numbers and expiry dates, quantity received, or supplied; and name and address of the supplier.</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>A procedure is followed for identification, collection, indexing, retrieval, storage, maintenance, disposal of and access to all applicable documents and records.</td>
<td></td>
</tr>
</tbody>
</table>

### Counterfeit products

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (*&quot;!&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>There is a procedure to handle counterfeit and suspected counterfeit products. It ensures that regulatory bodies and other relevant competent authorities and the holder of the marketing authorization for the original product are informed immediately in a case of confirmed or suspected counterfeiting of a pharmaceutical product.</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Counterfeit and suspected counterfeit products are kept secured, separately, clearly labelled and are not sold.</td>
<td></td>
</tr>
</tbody>
</table>

Continued
### Medicines quality assurance

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (“!” = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>A formal decision on the disposal of each counterfeit or suspected counterfeit product, ensuring that it does not reenter the market, is recorded.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Self-inspection</strong></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>An SOP, calendar and reports show evidence of self-inspections being conducted by independent, designated, competent persons.</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>There is evidence of management involvement and effective follow-up of corrective actions taken.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Complaints</strong></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>An SOP is followed for the handling of complaints distinguishing between different types of complaints, e.g. complaints about a product or its packaging, or complaints relating to distribution.</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>All complaints are thoroughly investigated, risk assessment is done and the root cause is identified. Appropriate action is taken. Records are maintained.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Recalls</strong></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>An SOP is in place to effectively and promptly recall products. A progress report and a final report on the recall is issued, which includes reconciliation between delivered and recovered quantities of products. This procedure is checked regularly and updated as required. The effectiveness of the arrangements for recalls is evaluated at regular intervals (e.g. mock recall).</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Recalled pharmaceutical products are segregated during transit and storage and are clearly labelled as such. They are kept under appropriate storage conditions.</td>
<td></td>
</tr>
</tbody>
</table>

**Comments:**

Total calculated for Module I
(e.g. total percentage divided by 33 if all 33 questions were rated):

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### MODULE II: Prequalification procedure

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>The prequalification procedure and standards used are based on the WHO-recommended procedures and guidelines. Key steps in prequalification have been defined and are followed meeting the recommendations in the MQAS.</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>The PA has a quality policy to ensure that prequalified products will be sourced – either through its own prequalification procedure, WHO prequalification, or products approved by stringent regulatory authorities (SRA). (Special note: Verify policy regarding products approved by SRAs for export only, as this may not always be appropriately controlled by the SRA).</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Procedures and records show that manufacturing sites comply with WHO good manufacturing practices (GMP) (or other internationally recognized GMP).</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>The persons responsible for prequalification and those responsible for purchasing are independent from another.</td>
<td></td>
</tr>
</tbody>
</table>

**Expression of interest (EOI) – public sector/non-commercial**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>Procedures and clear policies are followed for inviting, receiving and reviewing EOIIs. Records are maintained.</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>Detailed guidelines for the compilation and submission of information on products and manufacturing sites are publicly available.</td>
<td></td>
</tr>
</tbody>
</table>

**Product information, screening and evaluation**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>Product information is received in a suitable format with necessary contents such as a product dossier (detail as described by WHO, e.g. see Appendix 6 of the Model quality assurance system for procurement agencies.</td>
<td></td>
</tr>
</tbody>
</table>
Continued

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;1&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>Normally, a WHO-type certificate of a pharmaceutical product (CPP) is received with the product information. (If the formulation, strength or other specifications are different from the product for which the WHO-type product certificate (CPP) was issued, arguments and/or data to support the applicability of the certificate despite the differences are requested).</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>There is an appropriate system and infrastructure for the receiving and processing of product information. The screening of product information submitted is done according to an SOP and records are maintained. Written procedures are followed for evaluation. Evaluation reports are prepared for each product which includes a recommendation for acceptance or rejection. The evaluation and the report are done within appropriate time frames.</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Evaluators with suitable qualifications (e.g. in the pharmaceutical field) and experience (e.g. regulatory affairs) evaluate product data.</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Where appropriate (based on risk assessment) samples submitted together with product information packages are tested at laboratories meeting defined standards recommended by WHO.</td>
<td></td>
</tr>
</tbody>
</table>

**Inspections**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;1&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>There is appropriate evidence that active pharmaceutical ingredients (API) manufacturers are assessed for compliance with GMP (e.g. by finished pharmaceutical product (FPP) manufacturers).</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Inspections are planned and performed according to an SOP and plan, for FPP manufacturers.</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Audits are performed by suitably qualified, experienced auditors with relevant qualifications, training and experience.</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Waiving of audits is only done under appropriate, defined conditions. In case outcomes of inspections done by other authorities are recognized, such procedure is written and appropriate to ensure that GMP outcomes are reliable.</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>Audits cover all aspects of GMP as well as verification of data and information provided (e.g. in product data and site master file).</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>An audit report is prepared after each audit, containing detailed information and lists of deficiencies where relevant. Audit reports are communicated to manufacturers and a copy is kept as a record for a defined period of time.</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>Corrective actions to audit findings, and time lines for completing them are received, reviewed, and verified on site when necessary.</td>
<td></td>
</tr>
</tbody>
</table>

**Prequalification outcome**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;1&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>A written procedure is followed to finalize outcomes of the product evaluation and inspection (resulting in prequalification). Records are maintained on the process and decision taken. Manufacturers are informed of the outcome.</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>A list of prequalified products and manufacturers, based on the outcome of the evaluation of product data and information and manufacturing site inspections, is maintained. The list is product- and manufacturing site-specific and is reviewed regularly.</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>In case costs are recovered for prequalification, then these are defined in transparent procedures and are based on a fee-for-services structure. Manufacturers are notified of these in advance.</td>
<td></td>
</tr>
</tbody>
</table>

Comments:

Total calculated for Module II
(e.g. total percentage divided by 21 if all 21 questions were rated):
<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (“1” = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MODULE III: Purchasing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>Imported products enter through designated ports of entry as stipulated by national legislation.</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>Transparent SOPs are followed for procurement and purchasing, awarding contracts.</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>Suppliers are selected and monitored through a process that takes into account product quality, service reliability, delivery time and financial viability.</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>A written procedure is followed to handle donated products – and it ensures that products of known, appropriate quality are accepted and donated.</td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>A documented procurement quality system is in place covering purchase and procurement. Procedures are in place for: - the establishment of technical specifications; - quantification of requirements; - issuing of a tender (as appropriate); - selection of product(s) and manufacturer(s)</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>Responses to tenders as appropriate are examined by the relevant responsible persons to evaluate compliance with tender terms and conditions. There is evidence that awards are made to the maker of the lowest acceptable bid that meets these conditions.</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>Key activities in purchasing procedures are defined and include product selection and specification, product quantification, selection of suppliers and adjudication of tenders.</td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>An SOP is followed for the selection of products, and is based, where possible, on a national formulary or on the essential medicines list.</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>Procurement and tender documents list pharmaceutical products by their INN or national generic names.</td>
<td></td>
</tr>
<tr>
<td>64</td>
<td>Requests for products include quantities and required delivery dates.</td>
<td></td>
</tr>
<tr>
<td><strong>Monitoring of performance of prequalified manufacturers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>Procedures and records show that there is tracking and monitoring of: - the value of contracts awarded; - purchase and supply of prequalified products; - supplier performance; - product compliance.</td>
<td></td>
</tr>
<tr>
<td>66</td>
<td>Monitoring includes at least: - compliance with all of the contract terms and conditions; - sampling and testing; - supplied batches meet agreed specifications; - pharmacovigilance as required in the country; - complaints; - reinspection of manufacturing sites and reassessment of product information; - delivery schedules.</td>
<td></td>
</tr>
</tbody>
</table>

Comments:

Total calculated for Module III (e.g. total percentage divided by 12 if all 12 questions were rated).
**MODULE IV: Receiving – sampling and testing – storage**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (“!” = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>There is evidence that the products are stored at ports of entry under appropriate conditions; and as short as possible before being taken into stock.</td>
<td></td>
</tr>
<tr>
<td>68 !</td>
<td>SOPs are followed and records are kept for receiving, sampling, storage and handling of products (including quarantined, rejected, expired, recalled, returned products and suspected counterfeits expired stock).</td>
<td></td>
</tr>
<tr>
<td>69</td>
<td>There is sufficient space for the receiving and dispatch of products. Receiving and dispatch bays are separated and protect products from the weather.</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>Product containers are cleaned, if necessary, before taken into storage areas.</td>
<td></td>
</tr>
<tr>
<td>71</td>
<td>All incoming materials and products are received and checked in accordance with their SOP and quarantined until released (e.g. meeting specifications as per prequalified dossier, purchase order, certificate of analysis (CoA)).</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>Records for each delivery show description of the goods, quality, quantity, supplier, supplier’s batch number, the date of receipt, assigned batch number and the expiry date.</td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>Other procedures implemented include cleaning, pest control, containment and cleaning of spillages, prevention of contamination and cross-contamination; and waste removal. Programs and records are in place where appropriate.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Quality control</strong></td>
<td></td>
</tr>
<tr>
<td>74</td>
<td>There is a system in place for quality control of finished products procured (e.g. preshipment sampling, testing, and release or sampling, checks on shelf-life and labelling, testing when consignments are received).</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>Sampling plans which ensure that representative samples are taken for testing (used during receiving of consignments) are detailed in SOPs and are based on risk assessment. Qualified and experienced personnel review CoAs accompanying batches received.</td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>Adequate laboratory services are used to test products independently according to approved specifications and standards. The laboratory meets general requirements for good practices covering, e.g. facilities, policies and procedures, personnel, equipment, etc.</td>
<td></td>
</tr>
<tr>
<td>77</td>
<td>An SOP clearly describes the process and ensures that materials or products are not released for use until their quality has been judged satisfactory.</td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>Out-of-specification results are handled in accordance with an SOP for OOS investigation.</td>
<td></td>
</tr>
<tr>
<td>79</td>
<td>Products failing to meet their specifications are rejected in accordance with an SOP and documented evidence exists for the disposition of such products.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Storage</strong></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>Access to storage areas is controlled to ensure that no unauthorized person has access (24 hours a day, 7 days a week).</td>
<td></td>
</tr>
<tr>
<td>81</td>
<td>Separated areas are used for the storage of quarantined, rejected, expired, recalled, returned products and suspected counterfeits.</td>
<td></td>
</tr>
<tr>
<td>82</td>
<td>Storage areas have sufficient space and ventilation and fire control measures.</td>
<td></td>
</tr>
<tr>
<td>83</td>
<td>Temperature mapping of the storage areas was done in an appropriate manner.</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>Systems are in place to provide, control, monitor and record temperature (and relative humidity where required). Records of monitoring are kept for suitable periods of time. Appropriately calibrated devices (i.e. range, traceable to national standard) are used to monitor the temperature and relative humidity.</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>System/procedure (“!” = critical)</td>
<td>Rating</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>85</td>
<td>All products are stored in suitably protective, labelled containers; under appropriate storage conditions as specified on the labels.</td>
<td></td>
</tr>
<tr>
<td>86</td>
<td>Products that should be stored under specified cold conditions (requiring cold-chain) are handled appropriately during transport, delivery, receiving and storage. Temperature mapping studies were done for cold rooms; and power generators are available in case of power failure. Procedures are followed to ensure that ice packs are used in the correct manner in cold-chain boxes. Containers used for the transport are validated to ensure that cool products remain at the required temperature during transport.</td>
<td></td>
</tr>
<tr>
<td>87</td>
<td>! Narcotic and psychotropic substances/products are handled in accordance with national legislation and written procedures. These products are stored separately, where access is controlled and reconciliation is done monthly as well as each time stock is issued.</td>
<td></td>
</tr>
<tr>
<td>88</td>
<td>Miscellaneous and hazardous materials are handled in accordance with written procedures.</td>
<td></td>
</tr>
</tbody>
</table>

**Stock control**

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (“!” = critical)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>89</td>
<td>Stock rotation and control is maintained ensuring batch number control and expiry dating.</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>Periodic stock reconciliation is done (actual stock vs recorded stock). Significant stock discrepancies are investigated and results are documented in accordance with written instructions</td>
<td></td>
</tr>
<tr>
<td>91</td>
<td>Damaged containers are handled in accordance with written procedures. Any action taken is documented.</td>
<td></td>
</tr>
<tr>
<td>92</td>
<td>Regular checks are performed according to an SOP – to identify obsolete and outdated products. These are not issued/distributed.</td>
<td></td>
</tr>
<tr>
<td>93</td>
<td>Recalled materials are handled in accordance with a written procedure.</td>
<td></td>
</tr>
<tr>
<td>94</td>
<td>Returned goods are handled in accordance with a written procedure ensuring physical segregation and appropriate storage conditions. There is no possibility of entry of counterfeit products, or that the product quality is compromised.</td>
<td></td>
</tr>
<tr>
<td>95</td>
<td>Product returns and exchanges are done in accordance with terms and conditions of an agreement between the distributor and the recipient.</td>
<td></td>
</tr>
<tr>
<td>96</td>
<td>Returned products are transported in accordance with the relevant storage and other requirements.</td>
<td></td>
</tr>
<tr>
<td>97</td>
<td>An authorized person is identified to decide on the disposition of returned goods. The decision is based on, e.g. the nature of the product returned, special storage conditions required, its condition and history; and the time elapsed since it was issued.</td>
<td></td>
</tr>
<tr>
<td>98</td>
<td>There is a procedure for the appropriate destruction of products (complying with international, national and local requirements).</td>
<td></td>
</tr>
<tr>
<td>99</td>
<td>Records are maintained of all returned, rejected and/or destroyed products</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>Rejected goods are handled in accordance with an SOP, are stored separately (locked) and are marked accordingly. Access is controlled.</td>
<td></td>
</tr>
<tr>
<td>101</td>
<td>Waste materials are handled in accordance with a written procedure and are not allowed to accumulate. These are collected in suitable receptacles and disposed of safely and in a sanitary manner.</td>
<td></td>
</tr>
</tbody>
</table>

Comments:

Total calculated for Module IV
(e.g. total percentage divided by 35 if all 35 questions were rated):
### moduleName: Distribution of purchased products (Packaging – transport)

#### Containers and labelling

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (<em>1</em> = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>102</td>
<td>No repackaging or relabelling is done, unless licensed to do so, and the activities are found to meet international standards such as WHO GMP. (In such a case, repackaging and relabelling of products do not result in loss of identification and authentication of the products; and procedures are in place for the secure disposal of original packaging.)</td>
<td></td>
</tr>
<tr>
<td>103</td>
<td>Products are issued on a first-expiry-first-out (FEFO) basis.</td>
<td></td>
</tr>
<tr>
<td>104</td>
<td>Suitable packaging materials and containers are used that give protection and prevent damage of products. Damage is recorded, reported and investigated.</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>Containers bear labels (indicating handling, storage conditions, precautions, identification of contents and source). Where special transport and/or storage conditions are required, these are stated including any special legal requirements, safety symbols, etc.</td>
<td></td>
</tr>
<tr>
<td>106</td>
<td>Special care is taken when using dry ice in shipment containers.</td>
<td></td>
</tr>
<tr>
<td>107</td>
<td>Damaged and/or broken containers are handled according to procedures, also considering those that contained potentially toxic and hazardous products.</td>
<td></td>
</tr>
</tbody>
</table>

#### Dispatch

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (<em>1</em> = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>108</td>
<td>Dispatch and transportation is done after the receipt of a written, valid delivery order.</td>
<td></td>
</tr>
<tr>
<td>109</td>
<td>Written procedures for the dispatch are implemented, and cover, e.g. the nature of the product and special precautions.</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>Detailed records for dispatch are maintained which provide for traceability and facilitate recalls and investigation of counterfeits.</td>
<td></td>
</tr>
<tr>
<td>111</td>
<td>Written agreements with third-party carriers are in place if these are used.</td>
<td></td>
</tr>
<tr>
<td>112</td>
<td>Delivery schedules are prepared and suitable vehicles are selected.</td>
<td></td>
</tr>
<tr>
<td>113</td>
<td>Vehicles and equipment used to distribute, store or handle pharmaceutical products are suitable for their purpose and appropriately equipped.</td>
<td></td>
</tr>
<tr>
<td>114</td>
<td>Non-dedicated vehicles and equipment used are subjected to procedures which ensure that the quality of the pharmaceutical product is not compromised.</td>
<td></td>
</tr>
<tr>
<td>115</td>
<td>Vehicles and containers are loaded carefully and systematically. Where necessary, storage conditions are monitored, recorded and checked during transport. Devices/equipment used are appropriately calibrated.</td>
<td></td>
</tr>
<tr>
<td>116</td>
<td>Products with different status are kept separately during transport, e.g. rejected, recalled and returned products and are securely packaged, clearly labelled.</td>
<td></td>
</tr>
<tr>
<td>117</td>
<td>Procedures ensure that no unauthorized persons can enter/tamper with vehicles and/or equipment.</td>
<td></td>
</tr>
</tbody>
</table>

#### Transport and transit

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (<em>1</em> = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>118</td>
<td>Products and containers are secured to prevent unauthorized access, theft and other misappropriation of products during transportation.</td>
<td></td>
</tr>
<tr>
<td>119</td>
<td>Appropriate documentation accompanies products in transit.</td>
<td></td>
</tr>
</tbody>
</table>
| 120    | Procedures are in place to ensure that during transport:  
- the identity of the product is maintained;  
- the correct storage conditions are maintained;  
- there is no contamination of products;  
- precautions are taken against spillage, breakage, misappropriation and theft. |        |
Continued

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure (&quot;1&quot; = critical)</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>121</td>
<td>Deviations in storage conditions during transport are addressed, investigated and reported in accordance with an SOP.</td>
<td></td>
</tr>
<tr>
<td>122</td>
<td>Hazardous substances and other dangerous products are transported in safe, dedicated and secure containers and vehicles, and according to agreements and legislation.</td>
<td></td>
</tr>
<tr>
<td>123</td>
<td>Narcotics and other dependence-producing substances are transported in safe and secure containers and vehicles and in compliance with agreements and legislation.</td>
<td></td>
</tr>
<tr>
<td>124</td>
<td>Procedures are followed for cleaning spillages.</td>
<td></td>
</tr>
</tbody>
</table>

Comments:

Total calculated for Module V (e.g. total percentage divided by 23 if all 23 questions were rated):

MODULE VI: Reassessment

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>125</td>
<td>Procedures and records show that requalification is done at regular intervals. This includes reinspection of manufacturers and reevaluation of product information or data.</td>
<td></td>
</tr>
</tbody>
</table>

Reassessment of manufacturers

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>126</td>
<td>There is a procedure, programme (plan) and records that show reassessment of manufacturers taking place at least every three to five years. (This covers routine and non-routine assessment.)</td>
<td></td>
</tr>
<tr>
<td>127</td>
<td>A system is in place (e.g. agreement or SOP) ensuring that manufacturers inform the PA immediately of any changes to the manufacturing site or equipment that may have an impact on its prequalification.</td>
<td></td>
</tr>
<tr>
<td>128</td>
<td>A procedure is followed providing for suspension and withdrawal of a prequalified facility.</td>
<td></td>
</tr>
</tbody>
</table>

Reevaluation of products

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>129</td>
<td>Product information is reviewed routinely every three years or sooner if major changes occur.</td>
<td></td>
</tr>
<tr>
<td>130</td>
<td>There is a system in place (agreement/procedure) that ensures that manufacturers inform the procurement agency of any contemplated changes to the product that may affect its safety, performance, efficacy or quality.</td>
<td></td>
</tr>
<tr>
<td>131</td>
<td>A system is in place to review the requested changes (see above) and communicating approved changes to the procurement agency.</td>
<td></td>
</tr>
<tr>
<td>132</td>
<td>Non-routine reevaluation of products is done according to a procedure.</td>
<td></td>
</tr>
<tr>
<td>133</td>
<td>An SOP is used to manage variations to product information.</td>
<td></td>
</tr>
</tbody>
</table>

Monitoring of contracted-out services

<table>
<thead>
<tr>
<th>Number</th>
<th>System/procedure</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>134</td>
<td>Agreements are in place for activities contracted out such as storage, distribution, quality control, and are reviewed periodically.</td>
<td></td>
</tr>
<tr>
<td>135</td>
<td>There is evidence of compliance with a procedure for the monitoring of the performance of contractors and follow-up of non-compliance.</td>
<td></td>
</tr>
<tr>
<td>136</td>
<td>Management information shows continuous monitoring of performance of contractors which include tracking of cost, order and delivery status, lead-time and compliance with contract terms and conditions. Problems are reported and investigated with action taken.</td>
<td></td>
</tr>
<tr>
<td>137</td>
<td>On-site audits are done at intervals to verify compliance with standards, agreements and to verify source data where appropriate.</td>
<td></td>
</tr>
</tbody>
</table>

Comments:

Total calculated for Module VI (e.g. total percentage divided by 13 if all 13 questions were rated):
c) Model report format

Section 1: General information

| Name of organization: |  |
| Website reference: |  |
| Physical address: |  |
| Postal address: |  |
| Tel.: |  |
| Fax: |  |
| Contact person: |  |
| Email address: |  |
| Activities (tick all that apply): | Prequalification | Purchasing | Receiving and storage | Distribution |
| Date of inspection: |  |
| Products and/or services: |  |
| Inspector: |  |

Section 2: Summary

| General information about the procurement agent and site |  |
| History of inspections |  |
| Focus of the inspection and inspected areas |  |
| Summary of findings |  |
| General requirements for procurement agencies: |  |
| Prequalification: |  |
| Purchasing: |  |
| Receiving and storage: |  |
| Distribution (including the ability to supply the needed products in quantities required): |  |
| Reassessment: | Continued |
## Model report format, continued

### Outcome and conclusion

<table>
<thead>
<tr>
<th>Module</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module I: General requirements</td>
<td></td>
</tr>
<tr>
<td>Module II: Prequalification</td>
<td></td>
</tr>
<tr>
<td>Module III: Purchasing</td>
<td></td>
</tr>
<tr>
<td>Module IV: Receiving and Storage</td>
<td></td>
</tr>
<tr>
<td>Module V: Distribution</td>
<td></td>
</tr>
</tbody>
</table>
| Module VI: Reassessment | Level I: <60% (Not in compliance – unacceptable)  
Level II: 60% (Acceptable level of compliance)  
Level III: >80% (High level of compliance) |

**Comments:**

**Conclusion (Select and complete as appropriate):**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the self-assessment, including the observations listed above – the agency was considered to be operating at a high level of compliance with the MQAS for the following modules:……………...

And/or

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the self-assessment, including the observations listed above – the agency was considered to be operating at an acceptable level of compliance with the MQAS for the following modules:……………...

And/or

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the self-assessment, including the observations listed above – the agency was considered to be operating at an unacceptable level of compliance with the MQAS for the following modules:……………...

**Signature:** __________________________  **Date:** __________________________

**Name:** __________________________
Safety news

Unchanged recommendations

Testosterone: cardiac risk not confirmed

European Union – The European Medicines Agency (EMA) has reviewed available data from studies on testosterone-containing medicines, following concerns over serious side effects on the heart and blood vessels. Testosterone is used to treat hypogonadism (lack of testosterone produced by the body) in men. Available data do not provide consistent evidence that the use of testosterone increases the risk of heart problems in these patients, and hypogonadism itself may increase this risk.

The EMA recommended that testosterone-containing medicines should only be used where lack of testosterone has been confirmed by signs and symptoms as well as laboratory tests. The product information for these medicines will be updated to include this recommendation, together with warnings against use in men with severe heart, liver or kidney problems, and information that data on safety and effectiveness in patients over 65 years of age are limited and that age-specific testosterone reference values do not exist.

Clinical studies on the safety of testosterone are still ongoing, and their results will be considered in future regular benefit-risk assessments for these medicines. (1)

New Zealand – Medsafe’s Medicines Adverse Reactions Committee (MARC) has reviewed the available information about cardiovascular risks associated with testosterone therapy, and has found that the evidence of increased cardiovascular risk was not conclusive. The Committee recommended that marketing authorization holders should be requested to update the warnings and precautions section in the product information, and that general articles should be published to raise awareness of this risk. (2)


Agomelatine: strengthened advice to monitor liver function

European Union – The EMA has concluded its regular benefit-risk assessment of agomelatine (Valdoxan®, Thymanax®), used to treat major depression in adults, and has recommended measures to reiterate the importance of liver monitoring, the cornerstone for the safe use of agomelatine.

Agomelatine has a risk of severe side effects on the liver, especially in vulnerable patients. Nevertheless it remains a valuable treatment option in certain situations. Strengthened advice on liver function monitoring will be included in the product information, and a patient booklet will be distributed.

The current product information includes a warning that the medicine should not be used in patients aged 75 years or more. The EMA considered that available data
Safety news

who Drug Information Vol. 28, No. 4, 2014

does not justify upgrading of this warning to a contraindication.
   ► EMA News, 26 September 2014.

Restricted use

Intravenous nicardipine: only to control high blood pressure in specialist settings
United Kingdom – In agreement with the Medicines and Healthcare Products Regulatory Agency (MHRA), the marketing authorization holder of an intravenous nicardipine medicine has informed health professionals of the outcomes of a European regulatory review of intravenous nicardipine, initiated in 2012 at the request of the MHRA. The EMA had advised that these medicines should only be used to treat acute life-threatening hypertension and post-operative hypertension. Treatment should be administered by a specialist and in a well-controlled environment. Other uses are not recommended.

In adults, continuous infusion should be started at a rate of 3–5 mg/h. The rate can then be increased but should not exceed 15 mg/h, it should gradually be reduced when the target blood pressure is reached. Blood pressure should be monitored continuously during infusion and for at least 12 hours thereafter.
   ► MHRA Safety Communication, 12 September 2014.

Bromocriptine: not for premenstrual syndrome or benign breast disease
New Zealand – Medsafe has reviewed data on the efficacy and safety of bromocriptine when used to treat premenstrual symptoms and mastalgia. Available data provide insufficient evidence to recommend bromocriptine use for these indications, and information from its use of similar doses for other indications suggest that bromocriptine may cause fibrosis and impulse control disorders. Medsafe will therefore request the marketing authorization holder of bromocriptine to remove the above indications from the data sheet. (1)

Earlier, Medsafe had made recommendations on the safety and efficacy of bromocriptine for lactation suppression (2) in response to an EMA review started on the subject, and – as mentioned in the previous issue of WHO Drug Information – the EMA had recommended against the routine use of bromocriptine to stop lactation or to relieve pain or swelling of the breasts after childbirth (3).
   ► (1) Medsafe. Minutes of the 159th Medicines Adverse Reactions Committee Meeting - 11 September 2014.
   ► (2) Minutes of the 156th Medicines Adverse Reactions Committee Meeting - 5 December 2013.
   (3) EMA Press release, 21 August 2014.

Colistimethate sodium: reserve for serious infections resistant to standard antibiotics
European Union – Colistinin and colistimethate sodium (known as polymyxins) have been available since the 1960s, but have been in little use until they were brought back in recent years as an option to treat infections resistant to standard antibiotics. The EMA has reviewed the safety and effectiveness of injectable and liquid inhaled products containing colistimethate sodium.
The review concluded that injection or infusion of colistimethate sodium should be reserved for the treatment of serious infections caused by susceptible (i.e. aerobic Gram-negative) bacteria in patients whose other treatment options are limited. The medicine should be given with another suitable antibiotic where possible. Great caution is advised when using intravenous colistimethate sodium together with other medications that are potentially nephrotoxic or neurotoxic.

The Committee recommended that doses should always be expressed in international units (IU) to avoid medication errors, and proposed a conversion table for inclusion in the product information. Despite limited data the Committee recommended doses for use in patients with kidney problems and in children, and provided guidance on dosage for intraventricular or intrathecal or injection in adults, i.e. when the medicine is given directly into fluid surrounding the brain or spinal cord.

Valproate: not to be used in pregnancy

European Union – The EMA has recommended strengthening the restrictions on the use of valproate medicines due to the risk of malformations and developmental problems in children exposed to valproate in the womb.

Valproate should not be used to treat epilepsy or bipolar disorder in girls and in women who are pregnant or who can become pregnant unless other treatments are ineffective or not tolerated. Where valproate is the only option, women should use effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions.

In some countries valproate is authorized for the prevention of migraine. Pregnancy should be excluded before starting valproate treatment for migraine, and women should use effective contraception.

The EMA further recommended that educational materials should be provided to all healthcare professionals in the EU and to women who are prescribed valproate to inform them of these risks.

These strengthened restrictions are based on a review of available data as well as consultations with patients, affected families and experts.

Sulfur hexafluoride: not to be used with dobutamine in certain patients

United Kingdom – The marketing authorization holder, in agreement with the EMA and the MHRA, have informed health professionals that rare but severe and sometimes fatal arrhythmias have been reported in patients with cardiovascular instability undergoing stress echocardiography with sulfur hexafluoride (SonoVue®) in combination with dobutamine.

Sulfur hexafluoride is therefore contraindicated in combination with dobutamine in patients with conditions suggesting cardiovascular instability, e.g. recent acute coronary syndrome or clinically unstable ischaemia.

When administered alone, sulfur hexafluoride should be used in such at-risk patients only with extreme caution and after a careful risk/benefit assessment. Vital signs should be closely monitored during and after administration, because in these patients allergy-like and/
or vasodilatory reactions may lead to life-threatening conditions.

Sulfur hexafluoride is a contrast agent used in diagnostic procedures involving echocardiography and Doppler sonography.
► MHRA Safety Information, 1 October 2014.

### Safety warnings

**Ivabradine: heart problems**

**European Union** – The EMA has completed its review of ivabradine – used to treat heart failure and symptoms of angina – and has made recommendations aimed at reducing the risk of heart attack and bradycardia.

When used for angina, ivabradine should only be started if the patient’s resting heart rate is at least 70 beats per minute. Doctors should consider stopping treatment if there is no or only limited improvement in angina symptoms after three months.

Ivabradine should not be prescribed together with verapamil or diltiazem that reduce the heart rate, and patients should be monitored for atrial fibrillation. If atrial fibrillation develops during treatment, the balance of benefits and risks of continued ivabradine treatment should be carefully reconsidered.

**Carvedilol: Rare severe skin reactions**

**New Zealand** – The marketing authorization holder of carvedilol (Dilatrend®) has informed health professionals that very rare cases of severe cutaneous adverse reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported during treatment with the product, and that treatment should be permanently discontinued in patients who experience severe cutaneous adverse reactions possibly attributable to this medicine. The product information has been updated accordingly.
► Medsafe Safety information, sent 26 November 2014.

**Voriconazole: phototoxicity and squamous skin cancer**

**United Kingdom** – The marketing authorization holder, in consultation with the MHRA, has reminded health professionals that voriconazole (Vfend®) is associated with a risk of phototoxicity and skin squamous cell carcinoma. Voriconazole is used for the treatment of worsening, possibly life-threatening fungal infections and prophylaxis of invasive fungal infections in certain transplant recipients.

Health professionals are reminded to adhere to the advice given in the product information. If phototoxic reactions occur, they should refer the patient to a dermatologist and should consider stopping voriconazole treatment. If treatment is continued, the skin should be checked frequently and thoroughly, and voriconazole treatment should be stopped if precancerous skin lesions or squamous cell carcinoma are identified.

Voriconazole is also associated with a risk of liver toxicity. The UK product information (available at www.medicines.org.uk) has been updated with revised advice on monitoring liver function.
► MHRA Drug safety message, 10 October 2014.
**Immunoglobulins: rare but serious risk of blood clots**

**Canada** — Health Canada, in collaboration with marketing authorization holders, has informed health professionals of the risk of thromboembolic events in patients using non-hyperimmune immunoglobulins. Such events can occur regardless of dose or route of administration and in the absence of known risk factors. Canadian product monographs for all non-hyperimmune immunoglobulins (GamaSTAN® S/D, Gammagard Liquid, Gammagard S/D, Gamunex®, Hizentra®, IGIVnex®, Immune Serum Globulin (Human), Octagam® 5%, Octagam® 10%, and Privigen®) were updated to include thromboembolic events in the Serious Warnings and Precautions section.

▶ **Health Canada Advisory, 9 October 2014.**

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**Simeprevir: increased bilirubin may cause serious outcomes**

**Japan** — The Pharmaceutical and Medical Devices Agency (PMDA) has informed health care professionals that eight cases, including three fatal ones, of remarkably increased blood bilirubin in patients treated with simeprevir have been reported in Japan within 10 months following market authorization. Simeprevir is a recently approved medicine used in combination with other medicinal products for the treatment of chronic hepatitis C.

While the risk of increased blood bilirubin levels with simeprevir is known, the three deaths occurred after hepatic dysfunction and renal impairment to which the PMDA considers that hyperbilirubinaemia may have contributed.

The PMDA has requested that the product information should be updated to advise health professionals to test blood bilirubin regularly during simeprevir treatment and to monitor patients carefully even after simeprevir is stopped. Prompt action is important, as measures to avoid serious outcomes may be less effective once jaundice, general malaise and/or other symptoms occur.

▶ **PMDA Investigation results, 24 October 2014.**

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**Basiliximab: cardiac adverse events when used off-label in heart transplants**

**United Kingdom** — In agreement with the EMA and the MHRA, the marketing authorization holder has reminded health professionals that basiliximab (Simulect®) is indicated only for the prophylaxis of acute organ rejection in de novo allogeneic renal transplantation. Its efficacy and safety in other transplant indications have not been demonstrated.

In several small clinical trials in heart transplant recipients, serious adverse events such as cardiac arrest, atrial flutter and palpitations have been reported more frequently with basiliximab than with other induction agents. The warnings section of the Summary of Product Characteristics will be updated accordingly.

The communication follows a review by European drug regulatory agencies regarding the off-label use of basiliximab in heart transplants.

▶ **MHRA Drug safety message, 10 October 2014.**

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**Ustekinumab: serious skin conditions**

**Canada** — The marketing authorization holder, in consultation with Health Canada, has informed health professionals about rare reports of exfoliative dermatitis and erythrodermic
Psoriasis in psoriasis patients receiving ustekinumab (Stelara®). These skin conditions can occur within a few days of starting treatment, can be severe and can lead to hospitalization. Treatment with ustekinumab should be discontinued if a drug reaction is suspected, and the symptoms should be treated.

Exfoliative dermatitis can appear as redness and shedding of the skin over almost the entire area of the body, which may be itchy or painful. Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis as part of the natural course of their disease.

The product monograph will be updated to reflect this information. (1)

European Union – At its October meeting, the EMA’s Committee for Medicinal Products for Human Use (CHMP) adopted a safety variation to add the risk of serious skin conditions with ustekinumab to the Summary of Product Characteristics. Health professionals in the EU will be informed and the product information will be updated. (2)

Ponatinib: blood vessel blockage

European Union – The EMA has reviewed the benefits and risks of ponatinib (Iclusig®) and has recommended to include strengthened warnings about the risk of blood clots or blood vessel blockage in the product information. The risk is likely to be dose-related, although available data are not sufficient to make a formal recommendation on dose reduction.

Ponatinib is authorized for use in patients with chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia who cannot take or tolerate several other medicines of the same class.

The recommended starting dose should remain 45 mg of ponatinib once a day. The cardiovascular status of the patient should be assessed before starting therapy and regularly monitored during treatment.

Healthcare professionals should consider a dose reduction in patients with ‘chronic phase’ CML who are responding well to treatment, and who might be at particular risk of blood vessel blockage. Dose modifications or treatment interruption should be considered to manage treatment toxicity; if a reduced dose is used, patients should be monitored for maintenance of therapeutic response. Ponatinib should be stopped if there has been no response after three months of treatment. Patients should be monitored for high blood pressure or signs of heart problems.

Educational material will be provided to healthcare professionals, and a new study on the safety and benefits at lower doses of the medicine is planned.

Diclofenac and other NSAIDs: cardiovascular risks and liver damage

Australia – The Therapeutic Goods Administration (TGA) has reviewed a range of non-steroidal anti-inflammatory drugs (NSAIDs) and has found that the known risks at prescription-only dosages – high blood pressure, heart failure, heart attack and stroke, as well as liver damage in the case of diclofenac – also
apply to over-the-counter (OTC) forms of diclofenac, naproxen and ibuprofen. While the OTC products are safe at the recommended doses and for short durations, inappropriate use or overuse can pose a significant health risk. The TGA has reminded health professionals of prescribing recommendations for NSAIDs, and has encouraged them to educate patients on the signs and symptoms of serious cardiovascular toxicity and the need to seek medical attention immediately if they occur.

The recommendations are based on a review of cardiovascular risks associated with diclofenac, naproxen, ibuprofen, celecoxib, etoricoxib, indomethacin, meloxicam and piroxicam, as well as a full safety review of diclofenac. The TGA is exploring options to reduce the risks. (1)

Canada – The marketing authorization holders of systemic diclofenac products (Voltaren®, Arthrotec®), in consultation with Health Canada, have informed health professionals that at doses from 150 mg per day these products have a risk of heart problems and stroke that is comparable to that of COX-2 inhibitors (coxibs). The risk may increase with the dose and duration of use.

The maximum recommended daily dose for all indications has been reduced to 100 mg in product information and labelling of diclofenac-containing tablets and suppositories, except for Voltaren Rapide® which allows for a 200 mg dose only on the first day of treatment for dysmenorrhea. The lowest effective dose should be used for the shortest possible duration. COX-2 inhibitors and diclofenac are not recommended in patients with pre-existing cardiovascular disease (CVD) or cerebrovascular disease, or presenting risk factors for CVD. Treatment options other than NSAIDs, particularly COX-2 inhibitors and diclofenac, should be considered first in these patients. (2)

► (1) TGA Safety advisory, 7 October 2014.
(2) Health Canada Advisory, October 6, 2014.

Denosumab: osteonecrosis of the jaw and hypocalcaemia

United Kingdom – The manufacturer, in consultation with regulatory authorities, has warned that denosumab (Prolia®, Xgeva®) is associated with a risk of osteonecrosis of the jaw and hypocalcaemia. Denosumab is used to prevent bone complications in osteoporosis and certain types of cancer.

Treatment should not be started in patients due to undergo, or recovering from, oral surgery. Appropriate preventive dentistry is recommended before patients with risk factors for osteonecrosis of the jaw are given denosumab. During treatment, good oral hygiene and dental check-ups are encouraged.

The risk of hypocalcaemia increases with the degree of renal impairment. Before treatment existing hypocalcaemia must be corrected. Adequate calcium and vitamin D intake is important especially in patients with renal impairment.

Patients should immediately report any pain or swelling in the mouth, loose teeth, as well as any symptoms of hypocalcaemia.

► MHRA. Information sent to healthcare professionals in August about the safety of medicines. 2014.

Pregabalin: liver damage

Japan – The PMDA has informed health professionals that cases of fulminant hepatitis and hepatic dysfunction have
been reported in patients treated with pregabalin in Japan, including cases where causality could not be ruled out. Pregabalin is used for the treatment of neuropathic pain and fibromyalgia. The Agency recommended to revise the package insert to include these adverse events in the section on clinically significant adverse reactions.

While hepatic effects in patients taking pregabalin have also been reported to EU and WHO pharmacovigilance databases, the data do not support the conclusion that these adverse effects are associated with the use of pregabalin specifically.

► PMDA. Summary of investigation results. Pregabalin, 16 September 2014.

Zopiclone: next-day impairment

Canada – The manufacturer, in consultation with Health Canada, has informed health professionals of new dosage recommendations for the sleeping medication zopiclone (Imovane®) to minimize the risk of next-day impairment. This follows recommendations provided by the EMA for zolpidem and by the FDA for eszopiclone (see WHO Drug Information Vol. 28, No. 2, 2014).

The recommended starting dose of zopiclone has been reduced to 3.75 mg (one-half of the 7.5 mg tablet) at bedtime; the lowest effective dose for each patient should be used. The prescribed dose should not exceed 5 mg in elderly patients, in those with hepatic or renal impairment or in those being treated with potent CYP3A4 inhibitors. Dose adjustment may be needed if other CNS-depressant drugs are used at the same time. Patients should be informed of the risks and should wait at least 12 hours before driving or engaging in other activities requiring full mental alertness.


Bupropion: serious cardiovascular events

Australia – The TGA is adding strengthened warnings to product information for bupropion (Zyban® and other brand names) as serious cardiovascular adverse events have been reported with this medicine in Australia. The events included myocardial infarction, cerebrovascular accidents, and severe hypertension requiring acute treatment. A higher rate of hypertension was observed when bupropion was combined with nicotine transdermal patches. Bupropion is registered for use in Australia as a short-term adjunctive therapy, in conjunction with counselling and abstinence, to assist in smoking cessation.

The TGA advises that care should be taken when using bupropion, especially in patients with a recent history of myocardial infarction or unstable heart disease as there is limited information about the safety of bupropion in these patients. Blood pressure should be monitored during treatment, especially in patients with pre-existing hypertension, and consideration be given to stopping treatment if a clinically significant increase is observed.

► Medicines Safety Update, Volume 5, Number 5, October 2014.

Galantamine hydrobromide: serious skin reactions

Canada – The manufacturer, in consultation with Health Canada, has provided new safety information
about the risk of serious skin reactions associated with the use of galantamine hydrobromide (Reminyl ER®), used for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer’s type. Very rare cases of serious skin reactions including cases of Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and erythema multiforme have been reported with this medicine. Health care professionals should inform patients and caregivers about the signs of these serious skin reactions, and discontinue the medicine at the first appearance of skin rash. (1)

Japan – The PMDA has requested a revision of the package insert for galantamine hydrobromide (Reminyl®), to include acute generalized exanthematous pustulosis in the section on clinically significant adverse reactions of the package insert. The change was based on expert opinions and available evidence from reports of this adverse event in other countries. (2)

Australia – the marketing authorization holder has updated the product information for Reminyl® and other galantamine-containing products to reflect the risk of serious skin reactions. (3)

► (1) Health Canada Advisory, 18 November 2014.
(2) PMDA Summary of investigation results: galantamine hydrobromide, 20 November 2014.
(3) TGA Safety advisory, 8 December 2014.

Dimethyl fumarate: rare brain infection

United States – The U.S. Food and Drug Administration (FDA) has alerted health professionals and the public that a patient with multiple sclerosis who was being treated with dimethyl fumarate (Tecfidera®) developed progressive multifocal leukoencephalopathy (PML), a rare and serious brain infection, and later died. The patient had taken dimethyl fumarate for more than four years before the adverse event occurred.

The FDA decided to add information describing this case on the drug label and has advised that patients taking dimethyl fumarate should contact their health care professionals right away if they experience symptoms such as new or worsening weakness; trouble using their arms or legs; or changes to their thinking, eyesight, strength or balance. Health care professionals should stop dimethyl fumarate if PML is suspected.


Omalizumab: slightly increased risk of heart and brain adverse events

United States of America – An FDA review of safety studies suggests a slightly higher risk of problems involving the heart and blood vessels supplying the brain among patients being treated with the injectable asthma drug omalizumab (Xolair®) than in those who were not treated with the medicine. Information about these potential risks have been added to the drug label. Also, information about uncertain findings regarding a potential risk of cancer was added to the drug label.

Omalizumab is used to treat patients 12 years and older with moderate to severe persistent asthma and elevated immunoglobulin E levels, and those with chronic hives without a known cause, if these conditions cannot be controlled by other treatments. Health care professionals should periodically reassess
the need for continued therapy with omalizumab.
► FDA Drug safety communication, 26 September 2014.

**Risk minimization measures**

**Methylphenidate: web-based prescribing guide**

European Union – Following an EMA review of Ritalin® and other methylphenidate-containing medicines which called for the risk minimization measures (1), six MPH Marketing Authorisation Holders (MAHs) in the EU have collaborated in order to produce a web-based physician’s guide to methylphenidate prescribing (2).

Methylphenidate is part of a multi-modal treatment approach for attention deficit hyperactivity disorder (ADHD).

The website proposes checklists aiming to minimize the risk of cardiovascular, cerebrovascular, neuropsychiatric and growth disorders. Health professionals should review or complete these checklists before treatment starts and during therapy. The materials provided on the website should be used together with the full prescribing information for each individual product.


(2) Methylphenidate (MPH): physician’s guide to prescribing [web site]. Available at: http://www.methylphenidate-guide.eu/

**Medicines review started**

<table>
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<tr>
<th>Medicine</th>
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<th>Concerns</th>
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<tr>
<td>Dual anti-platelet therapy</td>
<td>Prevention of stent thrombosis and heart attacks</td>
<td>Preliminary clinical trial data have shown a higher overall risk of death with dual anti-platelet therapy for 30 months compared to 12 months. This risk was not observed in previous large trials.</td>
<td>► FDA, 16 November 2014.</td>
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<td></td>
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<td>► Health Canada Advisory, 18 November 2014.</td>
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Manufacturing quality issues

Health Canada restricts imports from various Indian sites
Canada – Health Canada has taken action to restrict imports of finished pharmaceutical products from Apotex Research Private Limited, active pharmaceutical ingredients (APIs) from Apotex Pharmachem India Pvt Ltd and from IPCA Laboratories, as well as products made with APIs from these sites (1).

Health Canada has also restricted the import of health products from three Micro Labs facilities in India: Bangalore, Goa and Hosur (2). Only products that are on authority’s “medically necessary” list will be allowed on the market, subject to prior testing by an independent third party.

In both cases, the regulatory action was triggered by data integrity concerns identified in inspections by international partners. The import ban is a precautionary measure. No specific safety issues have been identified with products already on the market, and neither Health Canada nor its regulatory partners have requested a recall of these products. Health Canada continues to work with regulatory partners to monitor compliance with good manufacturing practices at the sites.

World Health Organization – In June 2014 the WHO Prequalification Team had published on its website a notice of concern addressed to Micro Labs Ltd (3). To date the notice of concern has not been lifted. In August 2014 the prequalification team published information about WHO action taken regarding the deficiencies noted at the IPCA site (4).

(1) Health Canada Advisory, 30 September 2014.
(2) Health Canada Advisory, 27 October 2014.
(3) WHO Prequalification update, 6 June 2014.
(4) WHO Prequalification update, 14 August 2014.

Site review started

<table>
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<th>Facility</th>
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<tr>
<td>GVK Biosciences, Hyderabad, India</td>
<td>Contract research organization</td>
<td>Findings of non-compliance with good clinical practice. An inspection by the French medicines agency ANSM had raised concerns about study data used to support the marketing authorization applications of generic medicines. Some EU Member States have decided to suspend medicines marketing authorizations issued on the basis of studies conducted at the GVK Biosciences site.</td>
<td>EMA, 26 September 2014&lt;br&gt;WHO prequalification update, 7 August 2014&lt;br&gt;EMA Press release, 5 December 2014</td>
</tr>
</tbody>
</table>
Regulatory news

**Ebola**

**Update on treatments and vaccines**

The Ebola crisis has prompted an unprecedented cooperation between regulators to support WHO and to advise on possible pathways for the development, evaluation and approval of medicines to fight Ebola. Progress towards provision of treatments and vaccines is summarized below.

In August 2014, a WHO-convened panel had agreed unanimously that it is ethically acceptable to use of experimental medicines and vaccines under the exceptional circumstances of the Ebola epidemic (1). In early September, WHO convened a consultation on potential Ebola therapies and vaccines (2). The importance of supportive care and community response was stressed in this and subsequent discussions.

**Treatments**

In September, more than 200 experts from around the world met at WHO and agreed to prioritize convalescent blood and plasma therapies for further investigation. Many questions remain to be answered about the safety and efficacy of convalescent therapies, the feasibility of implementation in countries with shattered health systems, and the prospects of scaling up therapy to curb the fatality rate (2). To support implementation, WHO has issued new interim guidance on the use of convalescent therapies for national health authorities and blood transfusion services (3). The first clinical trials of – possibly curative – transfusions of whole blood or blood plasma from recovered patients have been scheduled to be conducted in Liberia, in line with WHO technical guidelines (4).

In September the European Medicines Agency (EMA) established an expert group to review available information on Ebola experimental treatments – excluding convalescent therapies – and invited developers to submit their data (5).

**Vaccines**

On 29–30 September, 70 experts attended a WHO-convened consultation on Ebola vaccines. They took stock of the many ongoing efforts to rapidly evaluate the safety and efficacy of Ebola vaccines for deployment as soon as possible to critical frontline workers and ultimately to populations at risk in mass vaccination campaigns. Two candidate vaccines have clinical-grade vials available for safety trials. (6)

In October, WHO convened industry leaders and key partners to discuss trials and production of Ebola vaccine (7). Consensus was achieved to make results available in December 2014, to begin efficacy trials at the same time, and to scale up production in 2015.

Also in October the EMA gave its first scientific advice on a development plan for an Ebola vaccine, using a new ‘rolling review’ procedure for data assessment and sharing of outcomes with healthcare decision-makers in affected countries (8).

At the time of writing, safety trials of vaccines were underway in the U.S., U.K., Mali and Switzerland, and about to begin
in Gabon, Germany and Kenya. The two Swiss trials are coordinated by WHO, with testing done on healthy volunteers, some of whom will be deployed in the fight against Ebola in West Africa (9).

At the meeting of the African Vaccine Regulatory Forum (AVAREF) in early November, delegates discussed collaborative mechanisms to fast-track clinical trial approvals and registration of Ebola treatments and vaccines in affected countries, and – importantly – reaffirmed the need to build stronger health systems (10).

Supportive care

Industry leaders and key partners have emphasized that community engagement remains key to fight Ebola and have called on local communities, national governments, NGOs and international organizations to scale up concerted activities urgently. (7). Meanwhile, a WHO-coordinated retrospective study has shown that supportive care, especially rehydration and correction of metabolic abnormalities, may contribute to patient survival (11).

Diagnostics

Quick and accurate diagnosis is key in fighting Ebola. WHO has launched two urgent initiatives to accelerate the delivery of rapid, sensitive, safe and simple Ebola diagnostic tests to West African countries. The first is a close collaboration of manufacturers, researchers, Médecins sans Frontières (MSF) staff, and the non-profit organization Foundation for Innovative New Diagnostics (FIND), and aims to support the development of suitable tests. The second is the establishment of an emergency rapid review mechanism for assessing a diagnostic’s quality, safety and performance. (12)

▶ (1) WHO Statement, 12 August 2014.
(2) WHO. Ebola situation assessment - 26 September 2014.
(3) WHO. Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks. Version 1.0, September 2014.
(4) WHO. Ebola situation assessment, 6 November 2014.
(5) EMA Press release, 26 September 2014.
(6) WHO. Experimental Ebola vaccines. 1 October 2014.
(7) WHO News release, 24 October 2014.
(8) EMA Press release, 29 October 2014.
(9) WHO News release, 6 November 2014.
(10) WHO Essential Medicines and Health Products. African regulators’ meeting looking to expedite approval of vaccines and therapies for Ebola [web page].

Clinical trials transparency

EMA adopts policy on publication of clinical reports

European Union – The EMA’s Management Board has unanimously adopted a new policy to publish the clinical trial reports that underpin the decision-making on medicines. The policy will enter into force on 1 January 2015 and will apply to clinical reports supporting all applications for centralized marketing authorizations submitted after that date.

According to the policy’s terms of use, the reports cannot be used for commercial purposes. In the limited instances
Pre-market assessment

EMA revises guidance on biosimilars

European Union – The EMA has published its revised guideline on biosimilars. The main change is that developers can now use a comparator product authorized outside the European Economic Area (EEA) in certain clinical studies and in non-clinical studies conducted in vivo. This new concept aims to avoid unnecessary repetition of clinical trials. The comparator must be authorized by a regulatory authority with similar rigorous scientific and regulatory standards to those of EMA, and the applicant must establish that the comparator is representative of the reference medicine authorized in the EEA.

A biosimilar is a biological medicine that is similar to an already authorized reference product (comparator). To obtain a marketing authorization the developer must demonstrate in studies that the biosimilar is as safe and effective as the reference medicine, and meets the EMA’s quality requirements.

While the revised guideline will come into force as of 30 April 2015, applicants can apply some or all of its provisions with immediate effect. Two related guidelines and procedural guidance are also being updated.

► EMA Press release, 29 October 2014.

EMA proposes harmonized clinical trials plan for vaccine in children

European Union – The EMA has proposed a single development plan for new tetanus-diphtheria-acellular pertussis vaccines that all pharmaceutical companies across the EU should follow. The proposal aims to avoid the duplication of similar clinical trials and the unnecessary exposure of children to clinical testing.

As the schedules of child vaccinations vary slightly between EU countries, a large number of fairly similar clinical trials are currently conducted in children when a new vaccine is being developed. The EMA collaborated with the European Centre for Disease Prevention and Control (ECDC) to define a single schedule for clinical trials. A panel of public health vaccinology experts have endorsed the proposal.

The proposed plan has been released for a three-month public consultation.

► EMA News, 23 September 2014.

EMA pilot to seek patient views on medicines risks and benefits

European Union – The European Medicines Agency (EMA) has launched a pilot project to involve patients in the assessment of the benefits and risks of medicines in its Committee for Medicinal Products for Human Use (CHMP). Patients will be invited to present their views on medicines for which there is an unmet medical need and where the Committee has doubts on its regulatory
decisions at any stage of the product life cycle. EMA has published a document outlining the principles of this approach.

The first active substance included in this pilot project has been afamelanotide, leading to the approval of a treatment for erythropoietic protoporphyria (EPP), a rare genetic blood disorder which causes an absolute intolerance to light (see also page 466).

The pilot project stems from a wider EMA strategy to involve patients in the Agency’s activities. It will run for at least one year, leading up to a proposal for full implementation.

► EMA Press release, 26 September 2014.

Australia to recognize EU conformity assessment for medical devices

Australia – New regulations will allow Australian manufacturers to obtain market approval for most medical devices based on conformity assessment certification from European notified bodies, the accredited organizations that carry out product assessments in the EU.

The highest risk devices such as those containing medicines or tissues of animal, biological or microbial origin, or Class 4 in vitro diagnostics (IVDs) including HIV tests, will still need TGA conformity assessment. The respective regulatory amendments are expected to be in place later this year.

► Australian Assistant Minister for Health, Media release, 15 October 2014.

Editor’s note: As the above media release mentions, regulators commonly adapt the level of control for IVDs to the level of risk that product deficiencies would pose for public health. IVDs (including products like tuberculosis or malaria IVDs, which are considered ‘low-risk’ in industrialized countries) are crucial in guiding treatment decisions for priority diseases. On the other hand, regulation of IVDs is still very limited or absent in many countries. Read more in WHO Drug Information Vol. 28, No. 3, 2014 on what WHO is doing to bring quality-assured IVDs to its Member States.

Pharmacovigilance

Canada passes Vanessa’s Law

Canada – The Government of Canada has passed modernized laws for drugs and medical devices. The Protecting Canadians from Unsafe Drugs Act, known as “Vanessa’s Law”, will enable the Government to recall unsafe medicines, impose tough penalties, compel pharmaceutical companies to make changes to products or do further testing, require mandatory adverse events reporting by health care institutions, and require transparency on regulatory decisions.

The Act introduces the most profound and important changes to the Food and Drugs Act in its fifty years of existence. It is named after an Australian Member of Parliament’s daughter who died of a heart attack while on a prescription drug that was later deemed unsafe and removed from the market.


EU project on using smartphones for drug safety information

European Union – The MHRA is leading a consortium of regulators, academics and the pharmaceutical industry in a three-year project, known as WEB-RADR, to develop new ways of gathering information on suspected adverse drug reactions (ADRs) using smartphones and social media. WEB-RADR will help to
develop recommendations on how these new tools should be used ethically and scientifically alongside existing drug safety monitoring systems.

The project is funded though the Innovative Medicines Initiative, a public-private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA).


**EMA expands public web access to reports on suspected side effects**

**European Union** – The EMA has added to its website information on suspected adverse drug reactions for an additional 1 700 active substances contained in medicines approved in the European Union (EU) by national authorities. The information comes directly from the EudraVigilance database. The web site was launched in 2012 and initially only contained adverse events information for centrally authorized medicines. Over the next few years it will be expanded to cover all medicines available in the EU.

Since July 2012 European pharmacovigilance legislation provides the possibility for patients to report side effects directly to the authorities in all EU Member States. Increasing numbers of patient reports are being received in the EudraVigilance database.

► EMA Press release, 6 October 2014.

**Australia, Switzerland create web portals to report adverse reactions**

**Australia** - The TGA has launched a new web-based service for consumers to report adverse events associated with medicines and vaccines.

In 2013 only about 3% of adverse events reports received by the TGA came from consumers. The new web site is part of TGA's activities taken in line with an international trend for regulators to encourage reporting by consumers. The TGA has also published a brochure outlining what and how to report, and is undertaking awareness activities and consumer research. (1)

Switzerland – With immediate effect, healthcare professionals and pharmaceutical companies can report suspected adverse drug reactions directly on the Internet through Swissmedic’s “ElViS” (Electronic Vigilance System) online reporting portal. Use of the portal is subject to registration on the ElViS website, and companies are also required to attend a Swissmedic training course. Data protection and security satisfy the most stringent requirements.

Swissmedic hopes that ElViS will result in more and better reports being received nearer to the event, helping to improve drug and patient safety in Switzerland. (2)

► (1) TGA News, 24 September 2014.

(2) Swissmedic Announcement, 6 October 2014.

**New MHRA guidance on reporting adverse drug reactions in children**

**United Kingdom** – The MHRA has announced new simplified guidance on how healthcare professionals should report suspected adverse drug reactions (ADRs) in children to its Yellow Card Scheme (mhra.gov.uk/yellowcard).

Recognizing that it is impractical to report all suspected ADRs in children, the new guidance asks that healthcare professionals report those reactions that are serious, medically significant or result
in harm, and those that are associated with newer drugs and vaccines, identified by a black triangle symbol in the Yellow Card Scheme. The guidance also places greater importance on the reporting of medication errors in children resulting in suspected ADRs, and explains the many reasons why monitoring of ADRs in children is particularly important.


**Organizations**

**Australia and New Zealand to keep separate regulatory authorities**
The Australian and New Zealand Governments have agreed to cease efforts to establish a joint therapeutic products regulator, the Australia New Zealand Therapeutic Products Agency (ANZTPA). The decision was taken after a review of progress and an assessment of the costs and benefits involved. The two countries will continue to co-operate on the regulation of therapeutic products. (1)

The New Zealand authority has announced that work will now be undertaken to strengthen the national regulatory scheme for therapeutic products. (2)

(2) Medsafe Media release, 20 November 2014.

**Veterinary medicines**

**EU proposes veterinary medicines legislation revisions**

European Union – The EMA has welcomed a major revision of the legal framework for veterinary medicines in the EU proposed by the European Commission. The revision includes measures to fight the development of antimicrobial resistance, notably by restricting the veterinary use of certain antimicrobials that are reserved for the treatment of infections in people. It also proposes streamlined marketing authorization procedures, simpler pharmacovigilance rules, better incentives for innovation, and clearer rules for internet retailing of veterinary medicines.

Other EU institutions will now consider the Commission’s proposals and will adopt their positions.

► EMA News, 10 September 2014.

**Sales of veterinary antibiotics in Europe decrease**

European Union – Sales of veterinary antibiotics have decreased by 15% according to the Fourth European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) report. Increased awareness of the threat of antimicrobial resistance as well as national programmes, campaigns and restrictions have been cited among the reasons for the decrease.

The ESVAC report is issued every year to inform antimicrobial policy and the responsible use of antimicrobials in EU Member States.

► EMA Press release, 15 October 2014.
Netupitant and palonosetron for chemotherapy-induced nausea

Product name: Akynzeo®
Class: Netupitant and palonosetron fixed-dose combination; ATC code: A04AA55
Approval: FDA
Use: Treatment of nausea and vomiting in patients undergoing cancer chemotherapy.
Benefits: Added effectiveness in preventing vomiting episodes in the acute, delayed and overall phases after the start of cancer chemotherapy, compared with oral palonosetron alone.

► FDA News release, 10 October 2014.

Naloxegol for opioid-induced constipation

Product name: Movantik®
Class: Peripherally acting opioid receptor antagonist; ATC code: A06AH03
Approval: FDA, EMA
Use: Oral treatment for opioid-induced constipation in adults with chronic non-cancer pain.
Benefits: Additional supportive care option to decrease the constipating side effects of opioids.
Safety information: The FDA is requiring a postmarketing study to further evaluate the potential risk of cardiovascular adverse events.

► FDA News, 16 September 2014.
► EMA/CHMP Summary of opinion, 25 September 2014.

Dulaglutide for type 2 diabetes

Product name: Trulicity®
Class: Glucagon-like peptide-1 (GLP-1) receptor agonist
Approval: FDA; EMA
Use: Once-weekly subcutaneous injection to improve glycaemic control in adults with type 2 diabetes.
Benefits: New treatment option for patients with type 2 diabetes who cannot be managed with first-line regimens. Can be used alone or added to existing treatment regimens.
Safety information: Dulaglutide should not be used in patients with diabetic ketoacidosis or those with severe stomach or intestinal problems. As thyroid C-cell tumours have been observed in rodent studies, dulaglutide should not be used in patients with a personal or family history of medullary thyroid carcinoma (MTC), or in patients with multiple endocrine neoplasia syndrome type 2 (which predisposes them to MTC).

► FDA News release, 18 September 2014.
► EMA/CHMP Summary of opinion, 25 September 2014.

Antihemophilic factor (recombinant), porcine sequence in acquired haemophilia A

Product name: Obizur®
Class: Porcine coagulation factor VIII
Approval: FDA (orphan drug designation)
Use: Treatment of bleeding episodes in adults with acquired hemophilia A (acquired factor VIII deficiency).
Benefits: Porcine Factor VIII is similar enough to human Factor VIII to be effective in blood clotting, but is less likely to be affected by the antibodies against human Factor VIII that are present in people with acquired haemophilia A.

► FDA News release, 24 October 2014.

Nonacog gamma in haemophilia B

Product name: Rixubis®
Class: Antihaemorrhagic, blood coagulation factor IX; ATC code: B02BD04
Approval: EMA
Use: Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) in patients of all age groups.
Benefits: Ability to prevent and treat bleeds in patients with haemophilia B including during surgery.
► EMA/CHMP Summary of opinion, 23 October 2014.

Afamelanotide for erythropoietic protoporphyria
Product name: Scenessé®
Class: Protective against UV radiation for systemic use; ATC code: D02BB02
Approval: EMA (orphan designation)
Use: Prevention of phototoxicity in adults with erythropoietic protoporphyria (EPP), a rare genetic disease causing intolerance to light.
Benefits: Afamelanotide stimulates the production of eumelanin, which naturally protects the skin against phototoxic reactions caused by sunlight, thereby significantly improving patients' quality of life.
Safety information: The company will implement a risk management plan and establish a registry of patients to collect safety and efficacy data.
Note: The approval was granted under exceptional circumstances, despite a lack of robust efficacy data due to the difficulties to recruit patients for placebo-controlled trials. Assessment was supported by data from the use of the medicine in compassionate use programmes globally. In addition, the EMA Committee heard feedback from patients and healthcare professionals involved in an expert group. This was the first time that patients were involved in EMA discussions on the benefits and risks of a medicine (see also page 461).
► EMA Press release, 24 October 2014.

Darunavir & cobicistat for HIV infection
Product name: Rezolsta®
Approval: EMA

Class: Antiretroviral fixed-dose combination; ATC code: J05AR14
Use: Treatment of human immunodeficiency virus (HIV) in antiretroviral therapy (ART)-naïve adults and ART-experienced adults with no darunavir (DRV) resistance associated mutations.
Benefits: Ability to provide sustainable virological suppression if given in combination with other antiretroviral medicinal products for treatment of HIV-1 infection.
► EMA/CHMP Summary of opinion, 25 September 2014.

Ledipasvir & sofosbuvir for hepatitis C infection
Product name: Harvoni®
Class: Fixed-dose combination of two direct-acting antivirals. Sofosbuvir is an NS5B inhibitor; ledipasvir – a new drug – is an NS5A inhibitor. ATC Code (temporary classification): J05AX65
Approval: EMA (accelerated assessment), FDA (priority review, breakthrough therapy designation)
Use: Treatment of chronic hepatitis C virus infection in adults.
Benefits: High cure rates in patients with chronic HCV infection without the need for treatments involving interferons. The latter are associated with poor tolerability and potentially serious side effects that rule out such treatment in a considerable proportion of HCV patients.
► EMA News, 26 September 2014.
FDA News release, 10 October 2014.

Dasabuvir for hepatitis C infection
Product name: Exviera®
Class: Antiviral agent, NS5B inhibitor. ATC code (temporary classification): J05AX16
Approval: EMA (accelerated assessment)
Use: Treatment of chronic hepatitis C in adults, in combination with other medicinal products.
Approved Benefits: Ability to inhibit viral replication in infected host cells which can lead to the eradication of the virus, correlating to a cure of chronic hepatitis C virus (HCV) infection, in both non-cirrhotic and compensated cirrhotic patients with genotype 1a/1b HCV infection.
► EMA/CHMP opinion, 20 November 2014.

Ombitasvir & paritaprevir & ritonavir for hepatitis C infection
Product name: Viekirax®
Class: Fixed-dose combination of two antiviral agents, inhibitors of NS5A (ombitasvir) and NS3/4A (paritaprevir), with ritonavir as a pharmacokinetic enhancer. ATC code (temporary classification): J05AX67
Approval: EMA (accelerated assessment)
Use: Treatment of chronic hepatitis C in adults, in combination with other medicinal products.
Benefits: Ability to inhibit viral replication in infected host cells which can lead to the eradication of the virus, correlating to a cure of chronic hepatitis C virus (HCV) infection, in both non-cirrhotic and compensated cirrhotic patients with genotype 1a/1b and 4 HCV infection.
► EMA/CHMP opinion, 20 November 2014.

Meningococcus B vaccine
Product name: Trumenba®
Class: Meningococcal Group B vaccine; ATC code: J07AH09
Approval: FDA (accelerated approval, breakthrough therapy)
Use: Prevention of invasive meningococcal disease caused by Neisseria meningitidis serogroup B in individuals 10–25 years of age.
Benefits: First licenced meningococcal group B vaccine in the U.S.; in addition to licenced vaccines for serogroups A, C, Y and W.
► FDA News release, 29 October 2014.

Pembrolizumab for advanced melanoma
Product name: Keytruda®
Class: Antineoplastic; PD-1 pathway blocker (first in class). ATC code (temporary classification): L01XC18
Approval: FDA (accelerated approval; breakthrough therapy, orphan product, priority review)
Use: Treatment of advanced or unresectable melanoma no longer responding to other drugs (ipilimumab, or ipilimumab and a BRAF inhibitor in patients whose tumors express a BRAF V600 mutation)
Benefits: Substantial improvement over existing therapies; shrinking tumours in approximately 24 percent of patients. Improvement on survival remains to be established.
Safety information: Potential for severe immune-mediated side effects that can involve healthy organs, including the lung, colon, hormone-producing glands and liver. In safety studies, such effects occurred uncommonly.
► FDA News release, 4 September 2014.

Ramucirumab for gastric cancer
Product name: Cyramza®
Class: Human receptor-targeted antibody that specifically binds VEGF Receptor 2 and blocks angiogenesis by binding of VEGF-A, VEGF-C, and VEGF-D.
Approval: EMA (orphan designation)
Use: Treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy. Ramucirumab can be used in combination with paclitaxel, or as monotherapy in patients for whom treatment in combination with paclitaxel is not appropriate.
Benefits: Ability to improve the survival in patients compared to chemotherapy alone (when used in combination with
chemotherapy) and compared to placebo (when used alone).
▶ EMA/CHMP Summary of opinion, 25 September 2014.

**Secukinumab for plaque psoriasis**

**Product name**: Cosentyx®

**Class**: Immunosuppressant; ATC code: L04AC10

**Approval**: EMA

**Use**: Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy

**Benefits**: More efficacious than placebo with respect to two co-primary endpoints in clinical studies.
▶ EMA/CHMP opinion, 20 November 2014.

**Pirfenidone for idiopathic pulmonary fibrosis**

**Product name**: Esbriet®

**Class**: Immunosuppressant; ATC code: L04AX05

**Approval**: FDA (fast track, priority review, orphan product, and breakthrough designations).

**Use**: Treatment of idiopathic pulmonary fibrosis

**Benefits**: Additional treatment option for patients with idiopathic pulmonary fibrosis, a serious, chronic condition. Current treatments include oxygen therapy, pulmonary rehabilitation, and lung transplant.

**Notes**: The FDA also approved nintedanib for the same use, see below. Pirfenidone was approved by EMA in 2011 under orphan designation.

**Safety information**: Not recommended for patients with moderate to severe liver problems. Can cause birth defects or death to an unborn baby; women who are able to get pregnant should use adequate contraception during and for at least three months after the last dose of treatment.
▶ EMA/CHMP Summary of opinion, 25 September 2014.
FDA News release, 15 October 2014.

**Nintedanib for non-small cell lung cancer / idiopathic pulmonary fibrosis**

**Product name**: EU: Vargatef®, Ofev®; U.S.: Ofev®

**Class**: Tyrosine kinase inhibitor anti-neoplastic agent, angiogenesis inhibitor.

**ATC code (temporary classification)**: L01XE31

**Approval**: EMA (orphan designation for Ofev®), FDA (fast track, priority review, orphan product, and breakthrough designations)

**Use**: Vargatef®: In combination with docetaxel, treatment of locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma tumour histology after first-line chemotherapy. Ofev®: Treatment of idiopathic pulmonary fibrosis.

**Benefits**: Vargatef®: Improvement in progression-free survival and overall survival compared to docetaxel plus placebo.

Ofev®: Additional treatment option for patients with idiopathic pulmonary fibrosis.

**Safety information**: Not recommended for patients with moderate to severe liver problems. Can cause birth defects or death to an unborn baby; women who are able to get pregnant should use adequate contraception during and for at least three months after the last dose of treatment.
▶ EMA/CHMP Summary of opinion, 25 September 2014.
FDA News release, 15 October 2014.

**Olaparib for a subtype of ovarian cancer**

**Product name**: Lynparza®

**Class**: Poly ADP ribose polymerase (PARP) inhibitor (first-in-class)

**Approval**: EMA (orphan designation)

**Use**: Monotherapy for the maintenance treatment of adult patients with relapsed, platinum-sensitive epithelial ovarian,
fallopian tube or primary peritoneal cancer carrying a BRCA gene mutation, and who have responded to platinum-based chemotherapy.

**Benefits:** Targeted treatment of a subtype of ovarian cancer for which limited treatment options are available.

► EMA Press release, 24 October 2014.

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**Blinatumomab for a rare form of acute lymphoblastic leukaemia**

**Product name:** Blincyto®

**Class:** Immunotherapeutic monoclonal antibody, T-cell engager

**Approval:** FDA (breakthrough therapy designation, priority review and orphan product designation)

**Use:** Treatment of relapsed or refractory Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukaemia.

**Benefits:** Potential for substantial improvement over available therapies. The manufacturer is required to conduct a study to verify that the drug improves survival.

**Safety information:** Boxed warning about the risks of low blood pressure and difficulty breathing (cytokine release syndrome) at the start of the first treatment, difficulty with thinking (encephalopathy) and other nervous system side effects. The medicine was approved with a Risk Evaluation and Mitigation Strategy, which consists of a communication plan to inform health care providers about the serious risks and the potential for preparation and administration errors.

► FDA News release, 3 December 2014.

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**Abuse-deterrent hydrocodone single-entity, extended release product**

**Product name:** Hysingla ER®

**Class:** Opioid analgesic

**Approval:** FDA (in line with guidance on abuse-deterrent properties)

**Use:** To treat pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

**Benefits:** The formulation is expected to reduce abuse by ingestion, snorting or injection.

**Safety information:** The product can still be abused or misused, and can then cause an overdose that may result in death. Additional postmarketing studies will be conducted to assess the effects of the abuse-deterrent features on the risk for abuse, and the consequences of that abuse in the community.

**Note:** This is the fourth extended-release opioid analgesic to be approved by the FDA with labelling consistent with the FDA's 2013 draft guidance on evaluation and labelling of abuse-deterrent opioids (after OxyContin®, Targiniq® and Embeda®).


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**Ketoconazole for Cushing’s syndrome**

**Product name:** Ketoconazole HRA®

**Class:** Antimycotic for systemic use; ATC code: J02AB02

**Approval:** EMA (orphan designation; accelerated approval of new indication)

**Use:** Treatment of Cushing’s syndrome

**Benefits:** Additional treatment option when surgery or other medicines fail or cannot be administered.

**Note:** Ketoconazole has been used “off-label” for more than 30 years to treat this rare and potentially life-threatening condition, although it has never been authorized for this indication in the EU.

**Safety information:** In July 2013, EMA recommended to suspend the marketing
authorizations of oral ketoconazole medicines to treat fungal infections due to the risk of liver injury. In the treatment of Cushing’s syndrome however, the benefits are greater than the risks, which can be managed by close monitoring of the patients’ liver function. The product is to be prescribed only by specialists as the posology needs to be individualized for each patient. Relevant information will be sent to healthcare professionals in the EU.

► EMA Press release, 26 September 2014.

Ulipristal emergency contraceptive without prescription

Product name: ellaOne®
Class: Emergency contraceptive; ATC code: G03AD02
Approval: EMA/CHMP recommendation, to be sent to the European Commission for a legally binding decision.
Use: To prevent unintended pregnancy. Must be taken within 120 hours (five days) of unprotected intercourse or contraceptive failure; works best if taken within 24 hours.
Benefits: Making the medicine available without prescription in the EU should speed up women’s access to the medicine and therefore increase its effectiveness.
Safety information: The safety profile of ulipristal is comparable to that of levonorgestrel-containing emergency contraceptives, which are already available without prescription in most EU countries and are registered for use up to 72 hours after unprotected intercourse or contraceptive failure.
Notes: If granted by the European Commission, the re-classification to non-prescription status would in principle need to be implemented by all EU Member States. Any exception regarding the non-prescription status of this medicine would fall within the responsibilities of the Member States.

Publications and events

Access to treatment

2014 Access to Medicines Index launched
Haarlem – The 2014 Access to Medicine Index, launched on 17 November, presents an updated ranking of the top 20 pharmaceutical companies. Key findings suggest that companies do more to improve access although progress is uneven, and that pricing strategies are increasingly tailored. On the other hand, 18 of the 20 companies have been the subject of settlements or judgements regarding breaches in ethical marketing, bribery or corruption standards or competition laws in the last two years.

The Access to Medicines Foundation, based in the Netherlands, is an international not-for-profit organisation dedicated to addressing the challenges of access to medicine worldwide. The Index is published every two years and gives insights into what the pharmaceutical industry is doing to improve the situation. The Index is funded by the Bill & Melinda Gates Foundation, the Dutch Ministry of Foreign Affairs and the UK Department for International Development.


WHO invites hepatitis medicines for prequalification
Geneva – WHO has expanded its list of medicines invited for prequalification to include treatments for hepatitis B and C. The 12th Invitation for Expression of Interest (EOI) related to HIV and AIDS-related medicines includes sofosbuvir, simeprevir and ribavirin formulations. An additional dosage strength for flucytosine is also included.

► WHO Prequalification update, 19 September 2014.

The lists of medicines invited for prequalification (HIV/AIDS including hepatitis B and C, Malaria, Tuberculosis,
Reproductive Health, Influenza, Zinc, and Neglected Tropical Diseases) are available at http://apps.who.int/prequal - Information for applicants - Invitations for Expression of Interest (EOI).

Antiviral Therapy special issue on access to HIV treatment

London – A special issue of Antiviral Therapy on the subject of ARV access in resource-poor countries has been published in partnership with UNAIDS. It includes articles on all aspects of these life-saving medicines: discovery and development, production, market and pricing, procurement and supply, effective use in treatment regimens, and delivery to patients.

The special issue includes a review of the regulatory framework for access to safe, effective quality medicines. The article points to the disparities in regulatory capacity and describes how WHO-prequalification and related initiatives have increased access to good quality medicines worldwide and – perhaps more importantly – are now laying the groundwork for collaborative approaches aiming to ensure that pharmaceutical products meet the same, stringent quality standards in all parts of the world.


Intellectual property

Interagency symposium on access to medical technologies

Geneva – The World Health Organization (WHO), World Intellectual Property Organization (WIPO) and World Trade Organization (WTO) have held their fourth trilateral symposium, titled “Innovation and access to medical technologies: challenges and opportunities for middle-income countries”.

Middle-income countries today include many countries with a poor public health situation for large parts of their population. The symposium aimed to identify ways to strengthen the capacity of governments to develop and apply policies that ensure access to new products while fostering an environment conducive to innovation.


WHO report on patent status of hepatitis medicines

Geneva – To help countries achieve equitable access to quality, effective, affordable and safe Hepatitis C treatments, WHO has published an analysis of the patent situation for seven new hepatitis treatments. The analysis, carried out by Thompson Reuters on behalf of WHO, provides crucial information about the patents themselves and the countries which they cover. This information is vital to inform government policies and actions when selecting and purchasing medicines for their populations.

► WHO publishes analysis of patent situation of new hepatitis treatments [web page]. Published 4 November 2014.
NIH and FDA win top award for meningitis vaccine licensing deal

Washington – The National Institutes of Health (NIH) and the FDA have received the “2014 Deals of Distinction Award” for the year’s most outstanding intellectual property licensing deal for technology transfer of a new, low-cost serogroup A meningitis vaccine named MenAfriVac.

According to WHO, 80–85% of all meningitis infections in sub-Saharan Africa are from group A. The vaccine has a low production cost and does not require constant refrigeration. The technology was licensed from the NIH Office of Technology Transfer to PATH, a Seattle-based non-profit leader in global health innovation, and then sublicensed to the Serum Institute of India (SII) under the Meningitis Vaccine Project, a partnership of PATH and WHO.

The deal has enabled the manufacture of MenAfriVac at an affordable cost for 26 African countries where serogroup A meningitis is most common. To date, more than 150 million people in 12 African countries have been vaccinated, with no reported cases of serogroup A meningitis in vaccinated populations.

Medicines for children

Improving medicines for children in Canada

Ottawa – An expert panel report released by the Council of Canadian Academies addresses the importance of developing safe and effective medicines for children. The panel advises that studying medicines in children is always possible and is in their best interests. The report was requested by the Minister of Health, on behalf of Health Canada.

Children respond to medicines differently from adults, and many of the medicines that they take have not been proven safe and effective in children. The panel found that in the U.S. and the EU paediatric medicines research is encouraged, required, and monitored in ways that offer lessons for Canada, and that, while paediatric medicines research is a Canadian strength, it requires reinforcement and sustained capacity and infrastructure to realize its full potential. The report stresses the need for collaboration across sectors and countries, and for tailored solutions reflecting the unique Canadian context.

This comprehensive, evidence-based assessment of the state of research and regulations on children’s medicines will serve as an important resource for policy-makers, regulators, health care professionals and researchers in the years to come. It is available both in English and in French.

Study shows better drug and antibiotic use where there is policy implementation

A study of public sector medicines use and prescribing indicators indicates that between 2002 and 2008 implementation of rational medicines use policies in countries is associated with better medicines use in the public sector. For example, there was less antibiotic use for upper respiratory tract infection in those countries that reported implementation of policies than in those that did not.
Data came from surveys on medicine uses conducted in primary health care facilities by various researchers according to a methodology and indicators established by WHO in collaboration with INRUD, and from WHO databases for 2002–2008 on implementation of 36 policy variables.

Suboptimal medicine use is a global public health problem. The findings highlight the importance of WHO’s core normative functions, which have come under threat in recent years. The authors emphasize the importance of recognizing the critical role of the WHO and of ensuring that its core functions are sustained and enhanced.


**WHO matters**

**Two WHO Expert Committee meetings held**

**Geneva** – The World Health Organization (WHO) Expert Committees are the highest technical advisory bodies to the WHO Director-General and Member States. Two Expert Committee meetings on medicines were held concurrently in Geneva on 13-17 October 2014.

At its forty-ninth meeting, the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) adopted a number of specifications, general texts and International Chemical Reference Standards for *The International Pharmacopoeia* (see pages 431 ff. for an example of a global specification). The Committee further adopted 16 technical supplements and eight guidelines for manufacturers and regulators, including new guidance on good review practice prepared under the leadership of the Asian-Pacific Economic Cooperation’s Regulatory Harmonization Steering Committee.

At its sixty-fifth meeting the WHO Expert Committee on Biological Standardization (ECBS) discussed standards and guidance related to inactivated polio vaccine, changes in manufacturing, good manufacturing practices for biological products and regulatory risk assessment. It also reviewed studies to establish international standards, including the first WHO reference reagent for anti-malaria (*Plasmodium falciparum*) human serum to support the development of a malaria vaccine.

Cross-cutting topics addressed by both Committees included collaboration and capacity-building platforms, regulatory pathways for approval of needed products, and systems to prevent and manage medicines shortages.

The guidelines adopted by the Expert Committees are published as annexes to the WHO Technical Report Series. The texts adopted at this year’s meetings will be presented to the WHO Governing Bodies in 2015 for information and final comments, and will then constitute WHO technical guidance recommended for implementation by WHO Member States and other parties.

► ECSPP: Guidelines are available at [www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines](www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines)

► ECBS website: [www.who.int/biologicals/expert_committee](www.who.int/biologicals/expert_committee)

**WHO prequalification of medicines 2013 annual report**

**Geneva** – The WHO Prequalification Team: medicines (PQTm) has published
its annual report for 2013. The year has seen a record number of products prequalified, including many ‘firsts’ of their kind. The prequalification teams for medicines, vaccines and diagnostics have been brought together within one WHO unit. A wide range of supporting activities, services and collaborative initiatives are ongoing to strengthen both prequalification and regulatory capacity in countries.

WHO currently has no regular budget to fund its prequalification activities. Financial support was received from UNITAID, which provided approximately 80% of the operational costs, from the Bill and Melinda Gates Foundation, and from the Global Fund, UNFPA and WHO’s Department of Neglected Tropical Diseases for procurement-related risk assessments by the Expert Review Panel (ERP). Although donor funding will continue, WHO is working towards a sustainable funding mechanism that will cover at least half of the operational costs for prequalification of medicines, diagnostics and vaccines.

In its 13 years of existence, PQTm has evolved into a global platform for regulators and manufacturers working together according to internationally recognized, harmonized quality standards. This enables them to cope with the challenges of today’s increasingly complex and globalized pharmaceutical markets. More support from the global community is needed to achieve broader impact in this crucial task.


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The International Pharmacopoeia

Flucytosinum
Flucytosine

This is a draft proposal for The International Pharmacopoeia (Working document QAS/14.599, December 2014).

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

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

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

Molecular formula. C₄H₄FN₃O

Relative molecular mass. 129.1

Graphic formula.

Chemical name. 5-Fluorocytosine; 4-amino-5-fluoro-2(1H)-pyrimidinone; CAS Reg. No. 2022-85-7.

Description. A white or almost white, crystalline powder.

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

Category. Antifungal.

Storage. Flucytosine should be kept in a tightly closed container, protected from light.

Additional information. Flucytosine melts at about 295°C.
Requirements

Definition. Flucytosine contains not less than 99.0% and not more than 101.0% of $\text{C}_4\text{H}_4\text{FN}_3\text{O}$, calculated with reference to the dried substance.

Identity tests

- Either tests A alone or tests B and C may be applied.

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

  B. The absorption spectrum of a 5.0 $\mu$g/mL solution in hydrochloric acid (0.1 mol/L) VS, when observed between 230 nm and 350 nm, exhibits a maximum at about 286 nm; the absorbance of a 1 cm layer at this wavelength is about 0.36.

  C. See the test described below under Related Substances, Test A. The principal spot obtained with solution (1) corresponds in position, appearance and intensity with that obtained with solution (2).

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to Method A using a platinum crucible; not more than 20 $\mu$g/g.

Clarity and colour of solution. Dissolve 0.5 g in carbon dioxide-free water R and dilute to 50 mL with the same solvent. This solution is clear and not more intensely coloured than standard colour solution Yw0 when compared as described under 1.11 Colour of liquids.

Sulfated ash. Determine the sulfated ash content as described under (2.3) using a platinum crucible; not more than 1 mg/g.

Loss on drying. Dry to constant weight at 105°C; it loses not more than 10 mg/g.

Fluorides. Prepare and store all solutions in plastic containers.

Prepare the following buffer solution. Dissolve 58 g of sodium chloride R in 500 mL of water R. Add 57 mL of glacial acetic R and 200 mL of a 100 g/L solution of cyclohexylenedinitrilotetraacetic acid R in sodium hydroxide (~40 g/L) TS. Adjust the pH to 5.0–5.5 with sodium hydroxide (~200 g/L) TS and dilute to 1000 mL with water R.

Prepare the following solutions. For solution (1) dissolve 1.00 g of the test substance in water R and dilute to 100.0 mL with the same solvent. For solution (2) dissolve 4.42 g of sodium fluoride R, previously dried at 120°C for 2 hours in water R to obtain a solution containing 1.9 mg fluoride ion per mL. Dilute solution (2) further to obtain standard solutions with the following concentrations: solution (3) 19 $\mu$g/mL; solution (4) 1.9 $\mu$g/mL; and solution (5) 0.19 $\mu$g/mL.

Add to 20.0 mL each of solution (1), (3), (4) and (5) 10.0 mL of the buffer solution and stir the solution using a magnetic stirrer and a plastic-coated stirring bar. Use a fluoride-ion-selective electrode and a silver/silver chloride reference electrode system, connected to a potentiometer capable of indicating reproducibly a minimum of ±0.2 mV. Insert the previously rinsed and dried electrodes into the solutions, stir for 5 minutes and read the potential in mV. Plot the logarithms of the fluoride ion concentration in solution (3), (4) and (5) versus the measured potential.

Determine the concentration of fluoride ion in solution (1), reading off from the standard curve the value of $\mu$g of fluoride ion per mL correlating with the measured potential and divide by the sample mass taken to obtain the content in the sample; not more than 200 $\mu$g/g.
Related Substances.
Either test A or test B may be applied.

A. Impurity A (fluorouracil) and impurity B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 60 volumes of nitromethane R, 20 volumes of methanol R, 10 volumes of ethyl acetate R and 10 volumes of water R as the mobile phase. Apply separately to the plate 1 μL of each of the following two solutions. Use a mixture composed of 60 volumes of methanol R, 35 volumes of water R and 5 volumes of glacial acetic acid R as the solvent. For solution (1) use 10 mg of the test substance per mL. For solution (2) use 10 mg of flucytosine RS per mL. Apply also 20 μL of each of the following two solutions. Use the same solvent as described above. For solution (3) use 20 mg of the test substance per mL. For solution (4) use 30 μg of fluorouracil RS per mL. After application allow the spots to dry in a current of cool air. Develop over a path of 9 cm in an unsaturated chromatographic chamber. After removing the plate from the chromatographic chamber allow it to dry exhaustively in a current of air. Examine the chromatogram in ultraviolet light (254 nm). Flucytosine, impurity A (fluorouracil) and impurity B are eluted with the following Rf values: flucytosine about 0.26, impurity A (fluorouracil) about 0.54 and impurity B about 0.74.

In the chromatogram obtained with solution (3) any spot corresponding to impurity A (fluorouracil) or impurity B is not more intense than the principal spot in the chromatogram obtained with solution (4) (0.15%).

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm x 4.6 mm) packed with base-deactivated particles of silica gel the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm).

As the mobile phase use a solution prepared as follows. Dissolve 13.6 g of potassium dihydrogen phosphate R in 950 mL of water R, adjust to pH 2.0 by adding phosphoric acid R and add 50 mL of methanol R.

Prepare the following solutions in a dissolution solvent prepared by dissolving 13.6 g of potassium dihydrogen phosphate R in 950 mL of water R and adding 50 mL of methanol R. For solution (1) use 0.3 mg of the test substance per mL. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration of 0.3 μg of flucytosine per mL. For solution (3) use 0.3 μg of fluorouracil RS per mL. For solution (4) mix 1.0 mL of solution (2) and 1.0 mL of solution (3).

Operate with a flow rate of 1.1 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 260 nm.

Inject separately 20 μL each of solution (1), (2), (3) and (4) and record the chromatograms for 15 times the retention time of flucytosine.

Use the chromatogram obtained with solution (3) to identify the peak due to impurity A (fluorouracil). Impurity B is eluted at a relative retention of about 12 with reference to flucytosine (retention time about 2.2 minutes).

The test is not valid unless the resolution between the peaks due to flucytosine and impurity A (fluorouracil) in the chromatogram obtained with solution (4) is not less than 5.0 and the symmetry factor for the peak due to flucytosine in the chromatogram obtained with solution (2) is not more than 2.0.
In the chromatogram obtained with solution (1):

- the area of any peak due to impurity A (fluorouracil) is not greater than 1.5 times the area of the corresponding peak obtained with solution (3) (0.15%);
- the area of any peak due to the impurity B, when multiplied by a correction factor of 0.6, is not greater than 1.5 times the area of the principal peak obtained with solution (2) (0.15%);
- the area of any other peak, other than the principal peak, is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%);
- the sum of the area of any peak corresponding to impurity A (fluorouracil), the corrected area of any peak corresponding to impurity B and the areas of all other peaks, other than the principal peak, is not greater than 3 times the area of the principal peak obtained with solution (2) (0.3%). Disregard any peak with an area less than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.03%).

**Assay**

Dissolve about 0.1 g, accurately weighed, in a mixture of 40 mL of acetic anhydride R and 100 mL of glacial acetic acid R1, and titrate with perchloric acid (0.1 mol/L) VS, determining the end-point potentiometrically. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 12.91 mg of $C_4H_4FN_3O$.

**Impurities**

A. 5-fluoropyrimidine-2,4(1H,3H)-dione (fluorouracil)

B. 2-ethoxy-5-fluoropyrimidin-4(3H)-one

**Reagent to be established**

Cyclohexylenedinitrilotetra-acetic acid R

trans-Cyclohexylene-1,2-dinitrilo-N,N,N',N'-tetra-acetic acid, $C_{14}H_{22}N_2O_8\cdot H_2O$.

*Description.* A white or almost white, crystalline powder.

*Melting point.* About 204°C.

***
Flucytosine intravenous infusion

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/14.600, December 2014).

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

**Description.** Flucytosine intravenous infusion is a clear, colourless or almost colourless solution.

**Category.** Antifungal.

**Storage.** Flucytosine intravenous infusion should be kept in a tightly-closed container, protected from light.

**Additional information.** Strengths in the current WHO Model List of Essential Medicines (EML): 2.5 g in 250 mL. Strengths in the current EML for Children: 2.5 g in 250 mL.

**Requirements**

Comply with the monograph for Parenteral preparations.

**Definition.** Flucytosine intravenous infusion is a sterile solution containing Flucytosine. It is supplied as a ready-to-use solution.

Flucytosine intravenous infusion contains not less than 90.0% and not more than 110.0% of the amount of Flucytosine (C\(_4\)H\(_4\)FN\(_3\)O) stated on the label.

**Identity tests**

- Either test A or tests B and C may be applied.
  
  **A.** Evaporate 10 mL of the infusion to dryness on a water-bath and dry the residue at 105 °C for about 1 hour. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from flucytosine RS or with the reference spectrum of flucytosine.

  **B.** Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 60 volumes of nitromethane R, 20 volumes of methanol R, 10 volumes of ethyl acetate R and 10 volumes of water R as the mobile phase. Apply separately to the plate 1 μL of each of the following two solutions. Use a mixture composed of 60 volumes of methanol R, 35 volumes of water R and 5 volumes of glacial acetic acid R as the solvent. For solution (A) use an aliquot of the infusion to be tested. For solution (B) use 10 mg of flucytosine RS per mL. After application allow the spots to dry in a current of cool air. Develop over a path of 9 cm in an unsaturated chromatographic chamber. After removing the plate from the chromatographic chamber allow it to dry exhaustively in a current of air. Examine the chromatogram in ultraviolet light (254 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).
C. The absorption spectrum (1.6) of the final solution prepared for Assay A, when observed between 230 nm and 350 nm, exhibits a maximum at about 286 nm and a minimum at about 245 nm.

**pH value (1.13).** pH of the infusion, 6.0–8.0.

**Pyrogens.** Carry out the test as described under 3.5 Test for pyrogens, per kg of the rabbit’s weight, 10 ml.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with base-deactivated particles of silica gel the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm).

As the mobile phase use a solution prepared as follows. Dissolve 13.6 g of potassium dihydrogen phosphate R in 950 mL of water R, adjust to pH 2.0 by adding phosphoric acid R and add 50 mL of methanol R.

Prepare the following solutions in a dissolution solvent prepared by dissolving 13.6 g of potassium dihydrogen phosphate R in 950 mL of water R and adding 50 mL of methanol R. For solution (1) dilute a quantity of the infusion to obtain a concentration of 0.3 mg of flucytosine per mL. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration of 0.3 μg of flucytosine per mL. For solution (3) use 0.3 μg of fluorouracil RS per mL. For solution (4) mix 1.0 mL of solution (2) add 1.0 mL solution (3).

Operate with a flow rate of 1.1 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 260 nm.

Inject separately 20 μL each of solution (1), (2), (3) and (4) and record the chromatograms for 15 times the retention time of flucytosine.

Use the chromatogram obtained with solution (3) to identify the peak due to impurity A (fluorouracil). Flucytosine is eluted at a retention time about 2.2 minutes.

The test is not valid unless the resolution between the peaks due to flucytosine and impurity A (fluorouracil) in the chromatogram obtained with solution (4) is not less than 5.0 and the symmetry factor for the peak due to flucytosine in the chromatogram obtained with solution (2) is not more than 2.0.

In the chromatogram obtained with solution (1):

- the area of any peak due to the impurity A (fluorouracil) is not greater than 5 times the area of the corresponding peak obtained with solution (3) (0.5%);

**Assay**

Dilute an accurately measured volume of the infusion with hydrochloric acid (0.1 mol/L) VS to give a solution containing about 0.1 mg per mL of Flucytosine. Dilute 5.0 mL of the resulting solution to 100.0 mL with the same solvent. Measure the absorbance of the resulting solution in a 1 cm layer at the maximum at about 286 nm. Calculate the content of Flucytosine \((C_4H_8FN_3O)\) using the absorptivity value of 70.9 \(A^{1\%}_{1cm} = 709\).

**Impurities**

The impurity limited by the requirements of this monograph is listed in the monograph for Flucytosine.
ATC/DDD Classification

ATC/DDD Classification (Temporary)

The following ATC codes and DDDs were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in October 2014. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology before 1 February 2015. If no objections are received before this date, the new ATC codes and DDDs will be considered final and included in the January 2016 version of the ATC/DDD Index.

New ATC 5th level codes:

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>asfotase alfa</td>
<td>A16AB13</td>
</tr>
<tr>
<td>ataluren</td>
<td>M03AX03</td>
</tr>
<tr>
<td>atazanavir and cobicistat</td>
<td>J05AR15</td>
</tr>
<tr>
<td>belinostat</td>
<td>L01XX49</td>
</tr>
<tr>
<td>benzyl alcohol</td>
<td>P03AX06</td>
</tr>
<tr>
<td>blinatumomab</td>
<td>L01XC19</td>
</tr>
<tr>
<td>brivaracetam</td>
<td>N03AX23</td>
</tr>
<tr>
<td>bupropion and naltrexone</td>
<td>A08AA62</td>
</tr>
<tr>
<td>ceftolozane and enzyme inhibitor</td>
<td>J01DI54</td>
</tr>
<tr>
<td>dasabuvir</td>
<td>J05AX16</td>
</tr>
<tr>
<td>dasabuvir, ombitasvir, paritaprevir and ritonavir</td>
<td>J05AX54</td>
</tr>
<tr>
<td>drospirenone</td>
<td>G03AC10</td>
</tr>
<tr>
<td>efinaconazole</td>
<td>D01AC19</td>
</tr>
<tr>
<td>emtricitabine and tenofovir alafenamide</td>
<td>J05AR17</td>
</tr>
<tr>
<td>emtricitabine, tenofovir alafenamide, elvitegravir and cobicistat</td>
<td>J05AR18</td>
</tr>
<tr>
<td>insulin deglucide and liagliptide</td>
<td>A10AE56</td>
</tr>
<tr>
<td>isavuconazole</td>
<td>J02AC05</td>
</tr>
<tr>
<td>lamivudine and raltegravir</td>
<td>J05AR16</td>
</tr>
<tr>
<td>lenvatinib</td>
<td>L01XE29</td>
</tr>
<tr>
<td>luliconazole</td>
<td>D01AC18</td>
</tr>
<tr>
<td>metformin and empagliflozin</td>
<td>A10BD20</td>
</tr>
<tr>
<td>nemonoxacin</td>
<td>J01MB08</td>
</tr>
<tr>
<td>nintedanib</td>
<td>L01XE31</td>
</tr>
<tr>
<td>nivolumab</td>
<td>L01XC17</td>
</tr>
<tr>
<td>obeticholic acid</td>
<td>A05AA04</td>
</tr>
<tr>
<td>octenidine</td>
<td>R02AA21</td>
</tr>
<tr>
<td>olodaterol and tiotropium bromide</td>
<td>R03AL06</td>
</tr>
<tr>
<td>ombitasvir, paritaprevir and ritonavir</td>
<td>J05AX67</td>
</tr>
<tr>
<td>papillomavirus (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)</td>
<td>J07BM03</td>
</tr>
<tr>
<td>pembrolizumab</td>
<td>L01XC18</td>
</tr>
</tbody>
</table>

Continued/
### ATC/DDD Classification (Temporary)

/Continued

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>pitolisant</td>
<td>N07XX11</td>
</tr>
<tr>
<td>rosuvastatin and valsartan</td>
<td>C10BX10</td>
</tr>
<tr>
<td>sebelipase alfa</td>
<td>A16AB14</td>
</tr>
<tr>
<td>sirolimus</td>
<td>S01XA23</td>
</tr>
<tr>
<td>smallpox, live attenuated</td>
<td>J07BX01</td>
</tr>
<tr>
<td>sofosbuvir and ledipasvir</td>
<td>J05AX65</td>
</tr>
<tr>
<td>sonidegib</td>
<td>L01XX48</td>
</tr>
<tr>
<td>tasimelteon</td>
<td>N05CH03</td>
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<tr>
<td>tedizolid</td>
<td>J01XX11</td>
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### 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>abarelix</td>
<td>3.6</td>
<td>mg</td>
<td>P</td>
<td>L02BX01</td>
</tr>
<tr>
<td>albiglutide</td>
<td>5.7</td>
<td>mg</td>
<td>P</td>
<td>A10BX13</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>13.3</td>
<td>mg</td>
<td>P depot</td>
<td>N05AX12</td>
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<tr>
<td>azilsartan medoxomil</td>
<td>40</td>
<td>mg</td>
<td>O</td>
<td>C09CA09</td>
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<tr>
<td>canagliflozin</td>
<td>0.2</td>
<td>g</td>
<td>O</td>
<td>A10BX11</td>
</tr>
<tr>
<td>cobicistat</td>
<td>0.15</td>
<td>g</td>
<td>O</td>
<td>V03AX03</td>
</tr>
<tr>
<td>daclatasvir</td>
<td>60</td>
<td>mg</td>
<td>O</td>
<td>J05AX14</td>
</tr>
<tr>
<td>dexamethasol</td>
<td>15</td>
<td>mg</td>
<td>O</td>
<td>N06BA11</td>
</tr>
<tr>
<td>lomitapide</td>
<td>40</td>
<td>mg</td>
<td>O</td>
<td>C10AX12</td>
</tr>
<tr>
<td>loxapine</td>
<td>9.1</td>
<td>mg</td>
<td>Inhal powder</td>
<td>N05AH01</td>
</tr>
<tr>
<td>misoprostol</td>
<td>0.2</td>
<td>mg</td>
<td>V¹</td>
<td>G02AD06</td>
</tr>
<tr>
<td>olodaterol</td>
<td>5</td>
<td>mcg</td>
<td>Inhal sol</td>
<td>R03AC19</td>
</tr>
<tr>
<td>peginterferon beta-1a</td>
<td>8.9</td>
<td>mcg</td>
<td>P</td>
<td>L03AB13</td>
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<tr>
<td>riociguat</td>
<td>4.5</td>
<td>mg</td>
<td>O</td>
<td>C02KX05</td>
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<tr>
<td>siltuximab</td>
<td>37</td>
<td>mg</td>
<td>P</td>
<td>L04AC11</td>
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<tr>
<td>simeprevir</td>
<td>0.15</td>
<td>g</td>
<td>O</td>
<td>J05AE14</td>
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<tr>
<td>sucroferric oxyhydroxide</td>
<td>1.5</td>
<td>g</td>
<td>O</td>
<td>V03AE05</td>
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<tr>
<td>vedolizumab</td>
<td>5.4</td>
<td>mg</td>
<td>P</td>
<td>L04AA33</td>
</tr>
</tbody>
</table>

*a Route of administration (Adm.R): O=oral; P=parenteral; V=vaginal; Inhal=inhalation

1) vaginal insert, refers to the content of one vaginal insert

2) delivered dose
ATC/DDD Classification (Final)

The following ATC codes, DDDs and alterations were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in March 2014. These are considered as final and will be included in the January 2015 version of the ATC/DDD Index.

**New ATC 5th level codes:**

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>ATC code</th>
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</thead>
<tbody>
<tr>
<td>asunaprevir</td>
<td>J05AE15</td>
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<tr>
<td>ceritinib</td>
<td>L01XE28</td>
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<tr>
<td>daclatasvir</td>
<td>J05AX14</td>
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<td>dasiprotimut-T</td>
<td>L03AX19</td>
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<tr>
<td>decamethoxine</td>
<td>D08AJ10</td>
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<td>evolocumab</td>
<td>C10AX13</td>
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<tr>
<td>fabomotizole</td>
<td>N05BX04</td>
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<tr>
<td>fimasartan</td>
<td>C09CA10</td>
</tr>
<tr>
<td>fluticasone furoate</td>
<td>R03BA09</td>
</tr>
<tr>
<td>ivermectin</td>
<td>D11AX22</td>
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<tr>
<td>linagliptin and empagliflozin</td>
<td>A10BD19</td>
</tr>
<tr>
<td>macimorelin</td>
<td>V04CD06</td>
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<tr>
<td>metformin and gemigliptin</td>
<td>A10BD18</td>
</tr>
<tr>
<td>mifepristone, combinations</td>
<td>G03XB51</td>
</tr>
<tr>
<td>siltuximab</td>
<td>L04AC11</td>
</tr>
<tr>
<td>sofosbuvir</td>
<td>J05AX15</td>
</tr>
<tr>
<td>susoctocog alfa</td>
<td>B02BD14</td>
</tr>
<tr>
<td>trifluridine, combinations</td>
<td>L01BC59</td>
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<tr>
<td>vorapaxar</td>
<td>B01AC26</td>
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</table>

**Change of ATC level name:**

<table>
<thead>
<tr>
<th>Previous</th>
<th>New</th>
<th>ATC code</th>
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</thead>
<tbody>
<tr>
<td>Sulphonamides, urea derivatives</td>
<td>Sulfonylureas</td>
<td>A10BB</td>
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</tbody>
</table>

**New DDDs:**

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>DDD</th>
<th>unit</th>
<th>Adm. R.</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>alemtuzumab</td>
<td>0.13</td>
<td>mg</td>
<td>P</td>
<td>L04AA34</td>
</tr>
<tr>
<td>benzydamide</td>
<td>9</td>
<td>mg</td>
<td>O</td>
<td>A01AD02</td>
</tr>
<tr>
<td>dextansoprazole</td>
<td>30</td>
<td>mg</td>
<td>O</td>
<td>A02BC06</td>
</tr>
<tr>
<td>fabomotizole</td>
<td>30</td>
<td>mg</td>
<td>O</td>
<td>N05BX04</td>
</tr>
<tr>
<td>granisetron</td>
<td>3.1</td>
<td>mg</td>
<td>TD</td>
<td>A04AA02</td>
</tr>
<tr>
<td>macitentan</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>C02XX04</td>
</tr>
<tr>
<td>sofosbuvir</td>
<td>0.4</td>
<td>g</td>
<td>O</td>
<td>J05AX15</td>
</tr>
<tr>
<td>vortioxetine</td>
<td>10</td>
<td>mg</td>
<td>O</td>
<td>N06AX26</td>
</tr>
</tbody>
</table>

*Route of administration (Adm.R): O=oral; P=parenteral; TD=transdermal*