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Rio de Janeiro, Brazil  
24 — 29 August 2014

http://www.anvisa.gov.br
WHO Prequalification of Medicines Programme

WHO launches the PQP Collaborative Registration Procedure

The Collaborative Registration Procedure (CRP) for WHO-prequalified products accelerates registration through improved information sharing between the WHO Prequalification of Medicines Programme (PQP) and national medicines regulatory authorities (MRAs).

The CRP aims to leverage the work of PQP during registration of WHO-prequalified medicines. It enables MRAs to utilize outcomes of PQP evaluations and inspections — thereby eliminating duplication of work, speeding up delivery of quality-assured products and making these more widely available. Since 2012, when the pilot phase began, fifteen MRAs in fourteen countries have decided to participate in the CRP and the present article describes experiences and lessons learned during the launch of this activity.

Given current resource constraints affecting pharmaceutical regulation in many regions of the world, international organizations increasingly rely on the rigorous standards of the WHO Prequalification of Medicines Programme (PQP) (1) and stringent regulatory authorities to ensure the quality, safety and efficacy of medicines that they fund or procure.

Although WHO prequalified medicines are evaluated and inspected according to international standards, they still have to be approved for use by national medicines regulatory authorities (MRAs) in the recipient countries.

The repeated assessment and inspection of medicines consumes scarce regulatory resources and extends the time needed to make them available to patients. In order to facilitate and accelerate registration, PQP has designed a procedure which helps to assure MRAs that WHO-prequalified medicines comply with high quality standards as documented in detailed reports of WHO evaluations and inspection results.

The WHO Collaborative Registration Procedure (CRP) (2) received final approval from the Sixty-sixth World Health Assembly in May 2013. Not only does the CRP enable MRAs to accelerate processing of registration applications for prequalified medicines, but it allows them to make use of work already carried out by PQP to strengthen their own regulatory oversight processes in line with international best practices.

The CRP has been published in the WHO Technical Report Series (3) and is open to all WHO Member States. Its principles can also serve as a model for other regulatory collaborative initiatives.

Principles

Participation of stakeholders is voluntary and MRAs wishing to participate agree:

• To respect the principles of the CRP.
• To treat proprietary information shared with PQP as confidential.
• To take a decision on CRP submissions for registration within 90 days of receiving access to confidential PQP outcomes of assessments and inspections.
Each MRA designates one or two focal points to communicate with PQP on a confidential basis. In the event that the CRP is activated for a specific pre-qualified product, focal points will be granted access to PQP's evaluation and inspection information through a secured Internet server.

Because PQP expertise outcomes shared within the terms of the CRP do not interfere with national decision-making processes, participation by MRAs may only require modification of regulatory procedures exceptionally. PQP has posted a list of participating MRAs on its web site.

The CRP is applicable only to medicines which have been subject to PQP evaluation and inspection and follows three steps.

• Firstly, a WHO prequalification holder wishing to register a prequalified product in a participating country should submit an application for registration to the MRA accompanied by an Expression of Interest (EOI) in which the company confirms that the product is technically the same as that prequalified, that submitted data correspond to the dossier as approved during pre-qualification and that it authorizes the MRA to communicate with PQP on product-related issues.

In parallel, the company authorizes PQP, in a pre-defined document, to share with the respective MRA the full outcomes of WHO's assessments and inspections confidentially through the PQP password-protected web site.

• Secondly, the MRA decides whether to apply the CRP to the specific submission — depending on whether it considers its execution to be expedient in the particular case — and informs PQP of its position. In the event that the MRA decides to make use of the CRP, PQP grants the focal point access to product-related assessment and inspection reports and other relevant documents providing detailed insight into the prequalification decision-making process and outcomes, including approved product specifications and the applicant's commitments. PQP is also prepared to provide additional explanations and responses to the MRA's questions. It is dependent on the discretion and resources of each individual MRA to decide whether the PQP outcome is recognized directly, whether it is considered for verification purposes, whether to organize a partial risk-based evaluation, or whether to use the shared data for quality assurance of its own independent assessment.

In any event, participating MRAs should issue a decision on each submission within 90 days of receiving access to confidential PQP outcomes of assessments and inspections.

• Thirdly, in line with the CRP, WHO and the applicant are informed of this decision within 30 days from when it is taken. The MRA is free to deviate from PQP opinion. However, deviations from WHO PQP conclusions should be explained and communicated to PQP. This process enables PQP to publish on its web site a list of those medicines that have been registered in participating countries under the same conditions as prequalified by PQP. For such products, it is possible to collaborate further with respective MRAs in product post-registration and product regulatory maintenance.

In the post-registration phase, stakeholders should work together to minimize differences between the nationally-registered and the WHO-prequalified product. Companies should submit the same variations to PQP and to participating MRAs, and the parties should inform each other of any major decisions regarding the product.
Information sharing
PQP does not share the full prequalification dossier with participating MRAs because the same technical data are submitted as part of the national registration process. Only assessment reports, variation reports and inspection reports are shared. Dossier assessment reports are in the form of PQP Quality Overall Summaries (QOS) — annotated with the assessor’s colour-coded remarks, requests for additional information and the applicant’s responses at each round of evaluation until prequalification.

Variation assessment reports are similarly annotated reports on changes to a prequalified product as per PQP variation guidelines. Inspection reports and signed-off Corrective and Preventive Action plans are shared for each manufacturing site of the finished product, as well as for those active pharmaceutical ingredient (API) manufacturing sites and clinical trial sites that PQP has inspected. PQP only shares data owned by the prequalification holder. Data provided by API manufacturers for the purposes of an active pharmaceutical ingredient master file (APIMF/DMF) procedure are not shared, unless there is a specific agreement with a data owner.

The MRA is free to use information to the extent it considers appropriate, subject to its participation agreement and confidentiality undertaking. Shared information enables the MRA to verify that the national submission conforms to WHO prequalification standards in all respects. In addition, examples of PQP process steps and documents followed in prequalifying each product may be useful for an MRA’s own training activities. Assurance that the regulatory status of the product remains in line with PQP conditions helps MRAs to define risk-based post-marketing surveillance measures that can be carried out in addition to PQP’s re-assessment and re-inspection. Quality control can be performed according to the same methods and specifications and in cooperation with other countries that have registered the product under the same conditions.

Experience
Ten MRAs participated in the pilot phase organized during the second half of 2012. Staff from seven of these MRAs have worked with PQP through rotational fellowships, while others have either participated in joint bi-monthly prequalification assessment sessions or other assessor training events offered by PQP. These regulators are largely familiar with PQP standards and procedures and have welcomed the opportunity to collaborate.

Since May 2013, the CRP is open to all WHO Member States. By October 2013, participation in the CRP had grown to 15 MRAs, including 12 in Africa that jointly cover more than 45% of the population of the WHO African Region. Three MRAs from Eastern Europe and Central Asia participate and others are considering participation.

PQP informs pharmaceutical companies about the CRP avenue for accelerated registration at its stakeholder meetings and training events, and provides information on its web site and in the standard letter sent upon acceptance of each product for prequalification and after prequalification is achieved. Several participating MRAs have also referred applicants to the CRP.

So far, fifteen prequalification holders have been in contact with PQP concerning collaborative registration of their medicines, including two prequalified “firsts” — zinc dispersible tablets and artemesunate + mefloquine fixed-dose combination tablets. Swift registration of these products in relevant countries will be of particular interest for international procurement. WHO has reached out to
additional MRAs in some potential target countries, inviting them to adopt and participate in the CRP.

Registration procedures
By October 2013, five prequalification holders had submitted a total of 29 EOI s for collaborative registration of 15 WHO-prequalified products (11 ARVs, one reproductive health product, two antimalarial and one second-line anti-TB product) in a total of seven countries. Participating MRAs agreed to apply the procedure in 18 cases. The most common reason for rejection was that already pending applications for registration in the respective country were at an advanced stage of evaluation.

Thirteen registration procedures were successfully completed for ten prequalified products (nine ARVs and one reproductive health product) through registration in six African countries (Ghana 5, Zimbabwe 3, Namibia 2, Kenya 1, Nigeria 1, Uganda 1).

Adherence to timelines
PQP had shared assessment and inspection information for the accepted EOI s within 0 to 42 days after receiving consent from the prequalification holder and confirmation of interest from the MRA (median: 10 days). The longest delays occurred early in the pilot phase while the confidential web site was undergoing upgrading.

MRAs adhered to the 90-day target timeline for eleven of the thirteen completed procedures (median time to registration 59 days). In seven cases the time taken was less than 60 days. More than 62 days were taken only in two cases (111 and 182 days) — one being due to awaiting the constitution of the relevant regulatory body. However, additional time was taken by MRAs to locate pending applications and identify their status, to respond to EOI s, to arrange access to the shared confidential web site and to provide feedback to PQP and applicants. Considering the above, total time taken from receiving access to confidential PQP outcomes of assessments and inspections to approval of 13 registered products ranged from 19 to 270 days (median: 99 days).

During the pilot phase, a substantial number of cases were initiated for applications which had already been pending for some time in the national registration system. Considering that 12 of the 18 submissions that the MRAs accepted to review under this procedure had been queued in national systems for a year or more, the collaborative procedure has saved time for all parties.

In Zimbabwe — where almost twice as many dossiers were received in 2012 than the registration system is designed to handle — the regulatory focal person states:

«The PQP Collaborative Procedure was a relief for us in Zimbabwe. ... From the pilot phase we established that approval within 90 days is do-able. ... The procedure allows us to save our meagre resources and focus them on risky products which have not been subjected to rigorous PQP quality assurance.» Head, Evaluations and Registrations Division, Medicines Control Authority of Zimbabwe.

Experience with specific aspects of collaboration
Product and data responsibility
In cases where the applicant for national registration is different from the holder of WHO prequalification, the latter must authorize the applicant to act on its behalf for the purposes of the CRP. This situation occurs quite commonly where the prequalification holder has delegated marketing of the product to another entity and/or where the MRA requires that the applicant for marketing authorization must be a local entity. PQP will typically be dealing with only one party, namely
that which authorizes it to share prequali-
fication information with the MRA. It is up to the company to define and manage any delegated responsibilities at additional levels.

**Format of national submissions**
Prequalification dossiers must be submitted in Common Technical Document (CTD) format. In a survey conducted by PQP in 2011, 15 out of 17 MRAs stated that they accept dossiers in CTD format. In most cases preparation of national submissions will require little additional effort by prequalification holders and technical data can be presented as approved by PQP. Wide use of the CTD format facilitates information-sharing under the CRP as well as promoting regulatory harmonization.

Abridged dossiers may be acceptable for MRAs wishing to reduce workload, given that detailed dossiers are on record at PQP and that technical advice on specific issues can be sought from PQP. Such special arrangements should always be confirmed to the applicant by individual MRAs. In any case, the MRA should make sure that it has sufficient technical information at its disposal to enable effective regulatory control. An example of this arose with a hormonal contraceptive that was submitted for registration in a version containing placebo tablets. The WHO-prequalified version contained tablets only with an active hormone.

**Dealing with product differences**
Some companies prefer to apply for national registration before being granted prequalified status. To ensure that the PQP product and technical data remain the same as that prequalified, the applicant is required to state any differences in its EOL and to upgrade the national dossier in line with the prequalified one. It can also happen that major variations have been approved for the already prequalified product and the dossier submitted in countries should be updated accordingly.

In practice, applicants have submitted upgrades in varying levels of detail and a range of approaches have been adopted by MRAs to deal with product data differences. For example, an MRA may decide to discuss pending prequalification variations with PQP before approving the products concerned, and request an applicant to re-submit upgraded dossiers.

The CRP was initially designed on the understanding that national applications would be submitted after completion of WHO-prequalification. The high number of CRP applications for pending submissions reflects a regulatory backlog in some countries. This will hopefully decline over time, as well as the strategy of making parallel submissions to PQP and national authorities at the same time.

Initial experience with handling of product differences highlights the importance of variation control once a prequalified product is registered in a country. Demonstrating that a product meets the same uniform international standards in different national markets offers a clear competitive advantage to prequalification holders. It is the responsibility of the applicant to ensure that the national registration status of the product reflects PQP adopted variations in line with regulations of the country.

Existing experience with management of post-prequalification and post-registration variations is still limited. Although the CRP provides principles for post-approval product maintenance and communication between PQP and MRAs, it has not been able to define a protocol due to the highly varying practices of MRAs. Effective management of variations in order to harness capacity of all parties is now a priority in further development of the CRP.

**Country-specific conditions**
PQP prequalifies products as being acceptable, in principle, for procurement by international organizations. However,
it is up to each MRA to evaluate the acceptability of a product in context. A recent example of this difficulty was noted when a prequalified artemisinin-based antimalarial combination treatment was registered in countries where it is not currently recommended in the national standard treatment guidelines. The situation was presented to the WHO Global Malaria Programme which proposed a registration strategy. While it is not PQP’s role to advise on the country-specific risks and benefits of using a product, the CRP provides a platform for discussion between the applicant, the MRA and WHO.

Benefits of the Collaborative Registration Procedure for key stakeholders

<table>
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<th>Manufacturers</th>
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<td>• Harmonized data for WHO prequalification and national registration.</td>
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<tr>
<td>• Facilitated interaction with MRAs in assessment and inspection.</td>
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<tr>
<td>• Accelerated and more predictable registration.</td>
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<td>• Easier post-registration maintenance.</td>
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<th>Procurers</th>
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<td>• Faster start to procurement processes and wider availability of PQ medicines.</td>
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<tr>
<td>• Access to status of a the same nationally registered and prequalified medicine (web site).</td>
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<tr>
<th>MRAs</th>
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<td>• Availability of WHO assessment and inspection outcomes to support national decisions and consolidate internal capacity.</td>
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<tr>
<td>• Opportunity to learn from PQP assessors and inspectors.</td>
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<tr>
<td>• Demonstration of MRA efficiency.</td>
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<tr>
<td>Confirming status of product to that prequalified.</td>
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<tr>
<td>Quality control using harmonized methods and specifications.</td>
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<td>Easier post-registration maintenance.</td>
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<tr>
<td>Easier problem management.</td>
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<td>Model of work-sharing.</td>
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<th>WHO</th>
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<tr>
<td>• Prequalified medicines are available faster to patients.</td>
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<tr>
<td>• Feed-back on WHO prequalification outcomes.</td>
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<th>Patients</th>
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<td>• Timely access to assured quality products.</td>
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communication has not been fully utilized. More work probably needs to be focused on enhancing user-friendliness of the IT system and seeking input from regulators.

The growing number of MRAs joining the CRP from different geographical regions also poses the question of language translation for CRP documents.

**Conclusion**
Experience and lessons learned show that a fully functional CRP can accelerate approval time, reduce workload and enhance the capacity and capability of MRAs in the registration process of WHO-prequalified products. Additionally, the CRP improves regulatory collaboration among MRAs — especially those interested in setting up worksharing networks at national and regional levels. The CRP provides benefits to all stakeholders while assuring international quality standards of the products in registering countries.

**Next steps**
At this stage of development, the CRP has progressed from a pilot to a fully operational phase. It is expected that new participating MRAs and manufacturers will bring additional experience which is relevant for the evolution of practical processes.

Good communication on technical issues, including effective post-approval control, will be crucial in sustaining successful implementation of the CRP. PQP will take every opportunity to meet with stakeholders and create a basis for effective communication. Regular meetings are scheduled with participating MRAs to cultivate use of the CRP and discuss ways to expand beyond its existing scope. Additional supporting documents are planned to be developed at these events.

Future challenges will include post-approval maintenance of registered medicines, cooperation on registration sample testing (which is still routine for some MRAs), and work-sharing in inspections — for example, ongoing collaboration on inspections with MRAs in the East African Community.

A frequent topic of discussion is how to expedite registration of medicines that have been approved by stringent regulatory authorities. The CRP provides certain helpful approaches that can be explored further.

**References**


Quality Assurance of Medicines

Review of the MQAS and preparation of a harmonized assessment tool for procurement agencies

In 2001, the World Health Organization (WHO) began development of the Model Quality Assurance System for Procurement Agencies (MQAS) which sets recommended standards for procurement agencies. In October 2005, following a consultative procedure, the MQAS guideline was adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) and published in 2006 (1).

Procurement agencies (PA) implementing the MQAS recommendations are routinely subject to assessment by customers — in many cases, using the PA’s own assessment tools to evaluate the potential service supplier. Due to the variety of standards used in assessment, the WHO–Global Fund (2) Joint Stakeholders meeting held in 2011 identified a need to revise the MQAS and develop a harmonized assessment tool that could be utilized by all. The aim was:

• To achieve a better use of resources.
• To coordinate PA assessments.
• To work towards mutual recognition of PA assessment findings.

A working group was created and comprised representatives of: QUAMED, Institut de Médecine Tropicale, Antwerp, Belgium; Partnership for Supply Chain Management (PFSCM); United Nations Children’s Fund (UNICEF); Médecins Sans Frontières (MSF); International Dispensary Association (IDA); Crown Agents; Global TB Drug Facility (GDF); Management Sciences for Health (MSH); International Union Against Tuberculosis and Lung Disease; United Nations Office for Project Services (UNOPS); United States Agency for International Development (USAID); International Committee of the Red Cross (ICRC), and the Committee for Medicinal Products for Human Use (CHMP).

An independent consultant was appointed in December 2011 to work with the group and the first working group meeting the took place on 12 March 2012. The group recognized the growing success of the MQAS and looked for ways to promote its further use. It was suggested to consolidate the MQAS by focusing on quality assurance aspects and communicating a message on the importance of maintaining quality throughout the supply chain. Development of a harmonized assessment tool would facilitate assessments and outcomes could be shared. This would lead to less duplication of inspection — of wholesalers, for example.

The next meeting was planned in Geneva in June 2012 and work on preparation of the assessment tool and revision of the MQAS continued. A meeting was also held with representatives of WHO to discuss the project and ways forward.

A draft assessment tool was launched as a pilot phase project in 2012 and several organizations were requested to comment. These included the Pan American Health Organization.


The Secretariat of the Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM) coordinated this project with the aim of preparing a harmonized assessment tool based on the WHO document: Model quality assurance system for procurement agencies (MQAS); WHO guidelines on good storage practices (GSP) and WHO Guidelines on good distribution practices (GDP).

The harmonized assessment tool was developed by a working group consisting of representatives from the following organizations: CHMP, Crown Agents, GDF, ICRC, IDÂ, MSF, MSH, PFSCM, QUAMED, UNICEF, UNION, UNOPS and USAID.

**Purpose**
The C assessment tool was developed by the working group with the objective of better using resources through coordination of procurement agency (PA) assessments and working towards mutual recognition of PA assessment findings.

The working group also felt that explanatory notes to supplement the tool would be helpful. In the subsequent months, further revision of the MQAS was undertaken and a new assessment tool in the form of an Aide Memoire was developed. Explanatory notes to support the Aide Memoire and a model inspection report were prepared. A small working group was appointed to revise the product questionnaire.

A final consultation took place in June 2013. Documents discussed included: the MQAS, assessment tool, Aide Memoire, format for an inspection report, interpretation guideline and the self inspection tool. The documents were then edited, circulated to all working group members and the ECSPP secretariat. WHO then published the documents and invited comments globally.

In October 2013, all revised documents with additional comments received were presented to the ECSPP. The documents were adopted and will be published in the forthcoming Expert Committee Report. The MQAS assessment tool Aide Memoire adopted by the ECSPP is set out below and on the following pages.

**Assessment tool based on the Model Quality Assurance System for Procurement Agencies: Aide Memoire for Inspections**

**Introduction**

The Secretariat of the Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM) coordinated this project with the aim of preparing a harmonized assessment tool based on the WHO document: Model quality assurance system for procurement agencies (MQAS); WHO guidelines on good storage practices (GSP) and WHO Guidelines on good distribution practices (GDP).

The harmonized assessment tool was developed by a working group consisting of representatives from the following organizations: CHMP, Crown Agents, GDF, ICRC, IDÂ, MSF, MSH, PFSCM, QUAMED, UNICEF, UNION, UNOPS and USAID.
Scope
The assessment tool is based on six MQAS modules:

- Module I: General requirements for procurement agencies
- Module II: Prequalification
- Module III: Purchasing
- Module IV: Receiving and storage
- Module V: Distribution
- Module VI: Reassessment

The tool covers these topics, as set out in the modules below: quality system and infrastructure of the PA under assessment, how the PA performed prequalification, purchasing of the products, receiving and storage. The last two modules focus on receipt of orders and dispatch of products, followed by the re-evaluation concept.

Harmonized assessment tool
The tool should be used by qualified, experienced persons when assessing PAs (including wholesalers and distributors) for compliance with recommended international standards. It can also be useful for a PA carrying out a self-assessment.

The tool is not a checklist but a document serving to remind inspectors what should be assessed during PA inspections.

Module I: General requirements for procurement agencies
This Module covers general requirements for procurement agencies including premises, equipment, transport and documentation (such as SOPs, confidentiality, code of conduct and complaint handling). It should be used in all cases of PA assessment. (Modules 2 to 6 may be used depending on the activities performed by the PA.)

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<th>Area of operation</th>
<th>Note</th>
<th>Critical aspects</th>
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| Premises, Equipment, Furniture, Transport | *General*  
  - Licensed to operate  
  - Sufficient space (offices for personnel, products, documents, samples, etc.)  
  - Suitable conditions  
  - Necessary furniture  
  - Working office equipment  
  - Stationery and consumables  
  - Telephone and email access  
  - Appropriate transport available | Compliance with legislation (licence)  
  There must be a sufficient and functional infrastructure to enable the PA to perform its activities |
| Human resources             | *Personnel*  
  - Compliance with national legislation (e.g., responsible person)  
  - Sufficient number of people  
  - Key personnel – quality assurance, prequalification, purchasing, storage and distribution  
  - Quality assurance/ prequalification and purchasing independent of one another  
  - Support staff  
  - Contracted personnel and agreements Training, education and experience | Compliance with legislation  
  Quality assurance/ prequalification and purchasing independent of one another (personnel – and reporting structure) |
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<th>Area of operation</th>
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<th>Critical aspects</th>
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<td><em>Code of conduct</em></td>
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<td><em>Confidentiality</em></td>
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<td>• Relevant product information kept confidential</td>
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<td>• Confidentiality agreements exist</td>
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<td>Computers</td>
<td><em>Appropriate hardware and software</em></td>
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<td>• Access control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Data transfer procedures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Reliable and accurate quality and management of data and information</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Data storage (e.g. hard copies)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Back-up at defined intervals, storage, access, readable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Virus protection programme and firewall</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Technical support</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Maintenance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Trained personnel</td>
<td></td>
</tr>
<tr>
<td>Financial systems</td>
<td>• Adequate banking facilities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Signatories of bank accounts appointed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Accounting system in place</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• National and international financial transactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Financial transactions performed without delay</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Funds available</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Regular financial audits are performed</td>
<td></td>
</tr>
<tr>
<td>Documentation</td>
<td><em>Comprehensive documented system</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Covers policies, guidelines, norms, standards, manuals, procedures,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• records and related documents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• SOPs for activities</td>
<td></td>
</tr>
</tbody>
</table>
### Quality Assurance of Medicines

<table>
<thead>
<tr>
<th>Area of operation</th>
<th>Note</th>
<th>Critical aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quality manual (QM)</strong></td>
<td>• Contains a quality policy</td>
<td>Activities and responsibilities described in SOPs which are implemented and followed; Records reflecting activities</td>
</tr>
<tr>
<td></td>
<td>• Evidence of QM implementation, QM maintained, reviewed and amended as necessary</td>
<td></td>
</tr>
<tr>
<td><strong>Standard operating procedures</strong></td>
<td>• SOP for writing an SOP followed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Written, clear, detailed SOPs for activities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Controlled, distributed and retrieved when required</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Available for use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• SOPs are reviewed periodically</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Quality risk management (QRM) principles applied</td>
<td></td>
</tr>
<tr>
<td><strong>Style and layout</strong></td>
<td>• SOPs in defined format</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Signed and dated</td>
<td></td>
</tr>
</tbody>
</table>

**Activities to be covered by SOPs**

- All activities should be covered by SOPs and include:
  - prequalification
  - purchasing
  - receiving and storage
  - distribution
  - training
  - handling of complaints
  - handling of recalls
  - document/record control including distribution and retrieval of SOPs
  - self-inspection
  - monitoring of environmental conditions (e.g. temperature)
  - monitoring supplier performance
  - identifying and reporting SSFFC medical products
  - evaluating offers received
  - ordering product(s) from supplier or manufacturer
  - change control
  - variations
  - corrective and preventive action (CAPA)

**List of prequalified products, manufacturers and suppliers**

- Current, authorized, access-controlled list
- Based on the outcome of evaluation
- Contains required information
- Product-, manufacturing site- and supplier-specific (where relevant)
- A key person responsible

**Change control**
### Module II: Prequalification

Prequalification is one of the key elements in ensuring purchase and supply of pharmaceutical products of acceptable quality. The prequalification process can be subdivided into two major parts, i.e., product-related assessment and manufacturer-related inspection.

<table>
<thead>
<tr>
<th>Area of operation</th>
<th>Note</th>
<th>Critical aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance of records</td>
<td>• Records of all operations kept&lt;br&gt;• Sufficient space for archiving&lt;br&gt;• Access controlled&lt;br&gt;• Retention period appropriate</td>
<td>Records are available for review</td>
</tr>
<tr>
<td>Contract arrangements</td>
<td>• Written contracts for delegated activities</td>
<td>Written, valid agreements in place</td>
</tr>
</tbody>
</table>

#### Principles
- Documented policy and procedures for prequalification
- Include assessment of product and manufacturers/suppliers
- If delegated – written agreement in place

#### Key persons and responsibilities
- Responsible personnel identified
- Independent from the purchasing personnel
- Job descriptions
- Communication between evaluation and inspections

**Evaluation of product information (_evaluators_)**
- List of evaluators
- Suitable qualifications and experience
- Job descriptions
- Contracted external evaluators used (confidentiality, conflict of interest and financial resources, references)

**Inspection of manufacturing sites (Inspectors)**
- List of inspectors
- Job descriptions
- Qualified, trained, experienced
- Contracted inspectors – confidentiality and no conflict of interest

<table>
<thead>
<tr>
<th>Area of operation</th>
<th>Note</th>
<th>Critical aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principles</td>
<td></td>
<td>Qualified, trained personnel perform prequalification activities (including assessment and inspections)</td>
</tr>
<tr>
<td>Key persons and responsibilities</td>
<td></td>
<td>Quality assurance/prequalification and purchasing independent of one another (personnel and reporting)</td>
</tr>
</tbody>
</table>
### Area of operation

<table>
<thead>
<tr>
<th>Key steps in prequalification defined</th>
</tr>
</thead>
</table>

#### Note

**Step 1. Soliciting information**
- Procedures for preparation of detailed, clear specifications; soliciting information; receiving and processing information
- Policy and procedure for handling late submissions
- Recording of data received
- Procedure for submitting product information publicly available and accessible
- Product information to be submitted defined (as a minimum, see product questionnaire)

**Step 2: Receive product information**
- Written procedures for receiving, identification, marking files, containers and samples, and sufficient space for unpacking and storage
- Procedure to ensure traceability of product information
- Personnel available

**Step 3: Screen product information**
- SOP: screen for completeness
- A screening form used
- Record of screening kept
- Outcome communicated to manufacturer/supplier

**Step 4: Evaluate product information**
- Follow SOP to evaluate against requirement
- Time frames
- Evaluation report for each product exists
- Outcome communicated to the manufacturer/supplier
- Response invited where needed
- Outcome accepted or rejected
- Evaluation report kept as record
- Samples analysed if needed (see also monitoring below)

**Step 5: Plan, prepare and perform inspections**

General points
- Evidence of GMP compliance
- Site of manufacture known
- Site inspection policy
- Contract manufacturing sites known

Control over active pharmaceutical ingredients (APIs) (inspection risk based)

#### Critical aspects

- Evaluation of product data and information as well as the criteria used to approve or reject a product
- Ensuring compliance with GMP
### Module III: Purchasing

Procurement should be carried out with the aim of purchasing effective, quality assured products and not be focused on price alone. The term “procurement” in this Module relates specifically to the purchase of health sector goods from manufacturers or suppliers. The module describes key activities in purchasing pharmaceutical products, as well as the recommended organizational structure of the procurement agencies which carry out these key activities.

<table>
<thead>
<tr>
<th>Area of operation</th>
<th>Note</th>
<th>Critical aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procurement</td>
<td>• Policy: suppliers are selected and monitored through a process that takes into account product quality, service reliability and performance, delivery time, ethics, legal status, financial viability and minimum order quantities</td>
<td>Purchasing prequalified products</td>
</tr>
<tr>
<td>Area of operation</td>
<td>Note</td>
<td>Critical aspects</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Procurement strategies (continued)                    | Purchase prequalified products (from manufacturers/suppliers)  
  • Efficient and transparent management  
  • Financial management procedures  
  • Competitive procurement methods  
  • Procedure to calculate lowest possible total cost  
  • Procurement and purchasing procedures are transparent  
  • Independent contract review  
  • Purchasing and tender documents list all pharmaceutical products by their international nonproprietary name (INN) or national generic names  
  • Intellectual property rights are respected in accordance with best practice and national law |                                                                                                                                                                                                                                                                                                                                                             |
| Procurement methods                                   | • Responses are responsive to the defined terms and conditions and are examined from invited suppliers  
  • Adjudication procedure  
  • Explicit criteria for awarding contracts  
  • Informed of the outcome  
  • Restricted tender  
  • Prequalified products and suppliers  
  • Competitive negotiation  
  • Direct procurement | Adjudication procedure and related records  
  Use a defined, transparent procurement method                                                                                                                                                                                                                                                                                                                                 |
| Key activities                                         | • Develop a list or catalogue of products (INN)  
  • Develop specifications for the products  
  *Quantification*  
  • Methods of product quantification  
  • Quantities purchased based on reliable estimate  
  *Procurement method*  
  • According to their policy and procedures |                                                                                                                                                                                                                                                                                                                                                             |
| Organization and responsibilities                     | • Personnel with appropriate qualifications and training  
  • Job descriptions  
  • Independent from those responsible for prequalification and quality assurance  
  • Procurement planned |                                                                                                                                                                                                                                                                                                                                                             |
| Monitoring performance of prequalified products, manufacturers/suppliers | • Procedure for continuous monitoring of performance of products, manufacturers and suppliers  
  Monitoring may include:  
  • review of quality control results |                                                                                                                                                                                                                                                                                                                                                             |
### Module IV: Receiving and storage

The procurement agency should ensure that pharmaceutical products purchased are received and stored correctly and in compliance with applicable legislation and regulations. Products should be received and stored in such a way that quality and integrity is preserved, batch traceability is maintained and stock can be rotated.

<table>
<thead>
<tr>
<th>Area of operation</th>
<th>Note</th>
<th>Critical aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>General arrangements</td>
<td>• Received and stored correctly</td>
<td>Procedures followed for receiving and storage</td>
</tr>
<tr>
<td></td>
<td>• Quality and integrity is maintained</td>
<td>Batch traceability</td>
</tr>
<tr>
<td></td>
<td>• Batch traceability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Stock rotation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Unidirectional flow</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Security of materials and products</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Subcontracting</td>
<td></td>
</tr>
<tr>
<td>Pre-shipment quality control</td>
<td>• Batches released by the manufacturer (certificate of analysis (CoA))</td>
<td>Batch release with CoA (meeting specifications)</td>
</tr>
<tr>
<td></td>
<td>• Batches additionally tested (risk-based approach) prior to shipment to PA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Selection criteria for quality control laboratory</td>
<td></td>
</tr>
<tr>
<td>Area of operation</td>
<td>Note</td>
<td>Critical aspects</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Receiving stock                       | • Receiving and dispatch bays  
• Incoming containers cleaned, quarantined  
• Review of CoAs  
• Released for use or distribution (responsible person involved)  
Checks on receipt:  
• order, delivery note, labels and transport conditions, integrity of packages and seals and uniformity of containers  
Visual inspection for:  
• contamination; tampering and damage; expiry date, compliance with labelling, packaging instructions  
• suspect containers and damaged containers – recorded and investigated | Goods received and checked according to an appropriate SOP – supported by records  
Products released by responsible person                                                                 |
| Post-procurement control              | • Random sampling for independent laboratory analysis  
• Selection criteria for quality control laboratory  
• SOP and national legislation  
• Representative samples – sampling plans and instructions (risk assessment)  
• Appropriately trained and qualified personnel | Action taken in case-of non-conforming product                                                                 |
| Rejected materials                    | • SOP for rejected products  
• Separate storage or validated computerized system  
• Action approved by authorized personnel and recorded | Rejected materials kept separately, access controlled and handled appropriately                      |
| Storage of materials/products         | **Personnel**  
• Trained  
• Personal hygiene and sanitation  
• Appropriate garments  

**Storage areas**  
• No unauthorized access  
• Sufficient space  
• Adequate ventilation, temperature and relative humidity  
• Conditions checked, monitored & recorded  
• Segregation of rejected, expired, recalled or returned stock  
• Toilet and washing facilities separated from storage areas  
• Narcotics/psychotropic medicines as per national legislation  
• SOP for fire control  
• No smoking and eating  
• SOP and records for cleaning  
• Waste management  
• Pest-control  
• SOP for handling spillages |
<table>
<thead>
<tr>
<th>Area of operation</th>
<th>Note</th>
<th>Critical aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage of materials/products (continued)</td>
<td><strong>Storage conditions</strong>&lt;br&gt;• As established by the manufacturer&lt;br&gt;• Orderly, batch segregation, stock rotation, first expired-first out (FEFO)&lt;br&gt;• Stored off the floor&lt;br&gt;• Space to permit cleaning and inspection&lt;br&gt;• Pallets in good state of cleanliness &amp; repair&lt;br&gt;• Stacking of products without damage&lt;br&gt;• Freeze-sensitive products – use monitoring devices&lt;br&gt;• Cold rooms (qualification, temperature mapping, alarm, monitoring, records, back-up system in case of failure)&lt;br&gt;<strong>Monitoring of storage conditions</strong>&lt;br&gt;• Temperature mapping protocol and report&lt;br&gt;• Calibrated sensors/devices&lt;br&gt;• Ongoing monitoring with records&lt;br&gt;• Out-of-limit and out-of-trend results investigated, action taken&lt;br&gt;<strong>Miscellaneous and hazardous materials</strong>&lt;br&gt;• Rodenticides, insecticides, fumigating agents and sanitizing materials&lt;br&gt;• Toxic substances and flammable materials</td>
<td>Access controlled and sufficient space&lt;br&gt;Appropriate conditions for storage</td>
</tr>
<tr>
<td>Re-packaging and re-labelling</td>
<td>• If performed – compliance with national legislation and WHO GMP</td>
<td>Compliance with national legislation and WHO GMP</td>
</tr>
<tr>
<td>Stock control</td>
<td>• Validated stock control system&lt;br&gt;• Batch number control and expiry dating&lt;br&gt;• Periodic stock reconciliation&lt;br&gt;• Significant stock discrepancies investigated&lt;br&gt;• Records maintained&lt;br&gt;• Damaged containers handled&lt;br&gt;<strong>Control of obsolete and outdated materials and products</strong>&lt;br&gt;• SOP&lt;br&gt;• Regular checks&lt;br&gt;<strong>Recalled materials and products</strong>&lt;br&gt;• SOP&lt;br&gt;• Written records of actions with signatures&lt;br&gt;• Products identified, recorded, reconciled and stored separately&lt;br&gt;• Decision by appropriately qualified and experienced member of staff&lt;br&gt;<strong>Returned goods</strong>&lt;br&gt;• SOP&lt;br&gt;• Quarantined and assessed&lt;br&gt;• Resale conditions&lt;br&gt;• Destruction in compliance with national requirements&lt;br&gt;• Records</td>
<td>Stock control in place (e.g., reconciliation, obsolete materials, recalled products, returned goods, FEFO and waste)</td>
</tr>
</tbody>
</table>
### Module V: Distribution

The PA (or contracted party) should have a well-managed distribution system meeting the objectives of ensuring constant supply of quality medicines. Distribution should be conducted in accordance with general principles of GMP.

<table>
<thead>
<tr>
<th>Area of operation</th>
<th>Note</th>
<th>Critical aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td>• Constant supply of medicines</td>
<td>Appropriate transport conditions</td>
</tr>
<tr>
<td></td>
<td>• Minimize medicines losses (spoilage and expiry)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Accurate inventory records</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prevent theft and fraud</td>
<td></td>
</tr>
<tr>
<td><strong>Transport conditions</strong></td>
<td>• Transport process has no negative impact on product</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Required storage conditions maintained</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Temperature excursions – risk assessment</td>
<td></td>
</tr>
<tr>
<td><strong>Cold chain</strong></td>
<td>• Validated process</td>
<td>Cold chain validated, maintained and monitored</td>
</tr>
<tr>
<td></td>
<td>• Applied where needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Appropriate containers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Packaging procedure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cooling agents used</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Calibrated monitoring devices</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Monitoring records reviewed, maintained</td>
<td></td>
</tr>
<tr>
<td><strong>Dispatch procedures</strong></td>
<td>• Compliance with legislation</td>
<td>Compliance with legislation</td>
</tr>
<tr>
<td></td>
<td>• Authorized recipients</td>
<td>Authorized recipients</td>
</tr>
<tr>
<td></td>
<td>• Procedures in place</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Special packaging requirements observed where needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dispatch and transport after receipt of a delivery order</td>
<td></td>
</tr>
<tr>
<td><strong>Dispatch containers</strong></td>
<td>• Provide protection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Appropriately labelled</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prevent theft (e.g., locked/wrapped)</td>
<td></td>
</tr>
</tbody>
</table>
Area of operation | Note | Critical aspects
--- | --- | ---
Dispatch records | • Detailed records kept (e.g., date, customer name and address; product name and batch number and quantity) • Products and batches traceable • Discrepancies investigated | Records ensure traceability of goods
Port of entry | • Storage conditions met • Temperature-sensitive products handled appropriately • Security measures in place (e.g., prevent theft, fraud and bribery) | 

**Module VI: Reassessment**
Quality of products and services should be continuously monitored. This process includes reassessment.

<table>
<thead>
<tr>
<th>Area of operation</th>
<th>Note</th>
<th>Critical aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reevaluation of manufacturers</td>
<td>• Reinspection frequency based on risk assessment • Within five-year cycle • Change control • Mechanism for suspension and withdrawal</td>
<td>Reinspection policy and procedure followed</td>
</tr>
<tr>
<td>Reevaluation of products</td>
<td>• Reevaluation procedure • Within five-year cycle • Variations procedure</td>
<td>Reevaluation of product policy and procedure followed</td>
</tr>
<tr>
<td>Monitoring performance of contractors</td>
<td>• Written procedure • Covers continuous monitoring, periodic review and renewal of contracts • System for documenting service problems</td>
<td></td>
</tr>
</tbody>
</table>

**References**
Safety and Efficacy Issues

Contaminated dextromethorphan

World Health Organization — On 24 January 2013, a WHO Drug Alert was issued following the discovery in Pakistan of two types of locally produced cough syrup containing the contaminated active pharmaceutical ingredient (API) dextromethorphan.

This incident led to the death of approximately 50 persons in Pakistan, all with a history of drug addiction, who had been abusing dextromethorphan-containing syrup for many years without any reported unexpected adverse reactions. The subsequent investigation found that manufacturers in Pakistan were obtaining the dextromethorphan API from a source in India.

Full laboratory testing of the dextromethorphan showed that it was contaminated with levomethorphan, the enantiomer of dextromethorphan, which is a potent opioid analgesic internationally controlled under Schedule 1 of the Single Convention on Narcotic Drugs (1961).

In January 2013, as a result of this incident, the Indian regulatory authorities suspended the manufacture, distribution, sale or use of the dextromethorphan in question.

WHO called on all countries to increase vigilance concerning dextromethorphan in general and to ensure that the API met all required quality specifications.

On 26 September 2013, WHO was notified of suspected drug intoxication involving eleven paediatric patients in Paraguay. All of the patients were experiencing influenza-like symptoms and had consumed medical products produced by a local manufacturer containing dextromethorphan. The children were aged from 2–9 years and serious adverse reactions included altered consciousness, cyanosis, respiratory distress and seizures. Onset of symptoms occurred from 2–7 hours after ingesting dextromethorphan. Since then, the number of patients experiencing adverse reactions rose to 44 confirmed cases, ranging in age from 5 months to 48 years. There was one fatality that may be linked to the event.

The Paraguayan Ministry of Health issued warnings concerning the medicines thought to be connected to this incident. Investigations by the Paraguayan authorities subsequently indicated the source of the API dextromethorphan to be the same Laboratories in India. The batch number of the dextromethorphan API used by the Paraguayan manufacturer was the same as one of the contaminated batches found in Pakistan. However, the Paraguayan manufacturer appears to have ordered the API in 2012, prior to events in Pakistan.

According to the local manufacturer in Paraguay none of the products have been exported, however they could possibly be available in neighbouring countries through local traders and travellers.

WHO advises extra vigilance for the API dextromethorphan and strongly urges that extreme caution be exercised by importing countries and manufacturers. Dextromethorphan should be carefully tested for the presence of the contaminant levomethorphan, and it should meet the recognized specifications.
Samples of contaminated dextromethorphan API from the original Pakistan incident have been analysed at the request of WHO and revealed limits of levomethorphan varying between 9.5% to 22.6%. All of the samples tested in both incidents have failed to comply with the requirements for the specific optical rotation as specified in the monograph for dextromethorphan hydrobromide published in *The International Pharmacopeia*.


**Falsified artemether and lumefantrine circulating in Cameroon**

**World Health Organization** — A *WHO Drug Alert* has been circulated concerning falsified batches of Coartem® that are circulating in Western and Central Africa. Coartem® is a fixed-dose artemisinin based combination therapy (ACT) (artemether 20 mg and lumefantrine 120 mg) used for the treatment of *Plasmodium falciparum* malaria. The genuine product is manufactured by Novartis and is a WHO prequalified medicine.

On 5 November 2013, Novartis informed WHO of further falsified versions of Coartem® recently circulating in Cameroon as follows:

- **Batch Number**: NOF 2153  
  **Manufacturing Date**: 01.2013  
  **Expiry Date**: 11. 2015
- **Batch Number**: F2929  
  **Manufacturing Date**: 01.2012  
  **Expiry Date**: 01.2016

The packaging of both batches is in English and bears the falsified green leaf logo of the Global Fund Affordable Medicines Facility – Malaria (AMFm) Programme.

Details of falsified batches of Coartem® circulated by WHO in May 2013 are as follows:

- **Batch number**: F1901  
  **Manufacturing Date**: 01.2012  
  **Expiry Date**: 01.2014

The packaging is in English and bears a falsified stamp of the Nigerian National Medicines Regulatory Agency, NAFDAC.

- **Batch Number**: F2261  
  **Manufacturing Date**: 01.2012  
  **Expiry Date**: 01.2014

The packaging is in English and bears the falsified green leaf logo of the Affordable Medicines Facility – Malaria (AMFm) Programme. Novartis has informed WHO that this batch has also been seen again recently in Cameroon.

All four batches are packaged for adult use and distribution within the public sector. The falsified batches contain little or no active pharmaceutical ingredient and are therefore ineffective.

Some of these batches have been found in a number of West and Central African countries in hospitals and street markets. Increased vigilance throughout the region is strongly advised. Hospitals, clinics, and pharmacies should check their stocks for these batches and report any suspicions to their national medicines regulatory authority.


**Ponatinib: increased reports of serious blood clots**

**United States of America** — The Food and Drug Administration (FDA) is investigating the increased frequency of reports of serious and life-threatening blood clots and severe narrowing of
blood vessels of patients taking ponatinib (Iclusig®). Health care professionals should consider whether the benefits of ponatinib treatment are likely to exceed the risks.

Ponatinib is used to treat adults diagnosed with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia or Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukaemia, who are no longer benefiting from previous treatment or who do not tolerate other treatment.

At the time of approval in December 2012, the Iclusig® label contained information about the risks of blood clots. In clinical trials conducted before approval, serious arterial blood clots occurred in eight percent of Iclusig®-treated patients and venous blood clots occurred in three percent of patients. In the most recent clinical trial data submitted by the manufacturer to FDA, at least 20 percent of all participants treated with ponatinib have developed blood clots or narrowing of blood vessels.

Data from clinical trials and postmarket adverse event reports show that serious adverse events have occurred in patients treated with ponatinib, including heart attacks resulting in death, worsening coronary artery disease, stroke, narrowing of large arteries of the brain, severe narrowing of blood vessels in the extremities, and the need for urgent surgical procedures to restore blood flow. Other problems include congestive heart failure and loss of blood flow to extremities resulting in tissue death requiring amputation. Newly identified serious adverse reactions have also been reported including decreased vision and clots in blood vessels of the eye. These adverse events were seen in all age groups treated and in those with and without cardiovascular risk factors.


Intravenous tigecycline: increased risk of death

United States of America — The Food and Drug Administration (FDA) is warning that an additional analysis shows an increased risk of death when intravenous tigecycline (Tygacil®) is used for approved or non-approved uses.

Healthcare professionals should reserve tigecycline for use in situations when alternative treatments are not suitable. Tigecycline is approved to treat complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia. Tigecycline is not indicated for treatment of diabetic foot infection or for hospital-acquired or ventilator-associated pneumonia.

In 2010, FDA informed the public that a meta-analysis of 13 Phase III and IV trials showed a higher risk of death among patients receiving Tygacil® compared to other antibacterial drugs. The increased risk was greatest in patients treated for ventilator-associated pneumonia, a use for which FDA has not approved the drug.

Since 2010, FDA has analysed data from ten clinical trials conducted only for FDA-approved uses showed a higher risk of death among patients receiving Tygacil® compared to other antibacterials. In general, the deaths resulted from worsening infections, complications of infection, or other underlying conditions.


Cinacalcet: hypocalcaemia and arrhythmia

Canada — A safety review of the drug cinacalcet (Sensipar®) has identified a possible link to arrhythmia associated with low blood calcium. Cinacalcet is used for treating disorders of the
parathyroid gland that result in abnormal blood calcium levels. It is well known to cause hypocalcemia and this risk is clearly outlined on the Canadian Sensipar® label.

Hypocalcemia can cause QT prolongation and arrhythmia which can be serious and may lead to sudden death. Stronger warnings have been added to the drug label to inform of the risk of QT prolongation and arrhythmia associated with use.

Healthcare professionals should prescribe cinacalcet with caution in patients with other risk factors for QT prolongation, such as known congenital long QT syndrome, or in patients who are taking other drugs known to cause QT prolongation. For patients treated with cinacalcet for chronic kidney disease and receiving dialysis, reduce dose or stop use if low blood calcium, signs of QT prolongation, or arrhythmia continue. For these patients, cinacalcet should not be started if they have severe hypocalcemia.


_ofatumumab and rituximab: reactivation of HBV infection_

**United States of America** — The Food and Drug Administration (FDA) has approved changes to the prescribing information for ofatumumab (Arzerra®) and rituximab (Rituxan®) to warn of the risk of reactivation of hepatitis B virus (HBV) infection. The revised labelling will also include additional recommendations for screening, monitoring and managing patients. Both ofatumumab and rituximab are used to treat certain cancers of the blood and lymph system. Rituximab is also approved to treat other medical conditions, including rheumatoid arthritis. Both drugs suppress the immune system.

In patients with prior HBV infection, HBV reactivation may occur when the body’s immune system is impaired. Infection can cause serious liver problems, including liver failure and death. The risk of HBV reactivation is already described in the labelling for both drugs; however, cases continue to occur, including deaths.


**Hydroxyethyl-starch solutions: only for hypovolaemia**

**European Union** — The European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC) has completed its review of hydroxyethyl-starch (HES) solutions following an assessment of new information and commitments from companies for additional studies and risk minimization activities. The Committee confirmed that HES solutions must no longer be used to treat patients with sepsis or burn injuries, or critically ill patients, because of an increased risk of kidney injury and mortality. HES solutions may, however, continue to be used in patients to treat hypovolaemia caused by acute blood loss, provided that appropriate measures are taken to reduce potential risks and that additional studies are carried out.

The review of HES solutions was initially triggered by the German medicines agency, the Federal Institute for Drugs and Medical Devices (BfArM), following studies showing an increased risk of mortality in patients with sepsis and an increased risk of kidney injury requiring dialysis in critically ill patients following treatment with HES solutions.

Artesunate: haemolytic anaemia

World Health Organization — Injectable artesunate is a life-saving therapy for patients with severe Plasmodium falciparum malaria and provides a substantial reduction of mortality. In the two largest randomized controlled trials conducted in patients with severe malaria, parenteral artesunate treatment reduced deaths by 34.7% (Asia) and by 22.5% (Africa) compared with parenteral quinine. WHO currently recommends artesunate (intravenous or intramuscular) as the first line treatment for the initial management of severe malaria.

A number of cases of delayed haemolytic anaemia have been identified following treatment of severe malaria with injectable artesunate. In March 2013, the Medicines for Malaria Venture (MMV) convened a meeting of experts to review the available evidence on delayed haemolytic anaemia following treatment with injectable artesunate.

The full report of the expert meeting is now available on the MMV web site together with an information note which reflects the current WHO position based on the outcome of the review meeting and consultation with the GMP Technical Expert Group on Malaria Chemotherapy.


Opioid analgesics: new safety warnings

United States of America — The Food and Drug Administration (FDA) has announced class-wide safety labelling changes and new postmarket study requirements for all extended-release and long-acting (ER/LA) opioid analgesics intended to treat pain.

The updated indication states that ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

The updated indication further clarifies that, because of the risks of addiction, abuse, and misuse, even at recommended doses, and because of the greater risks of overdose and death, these drugs should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain; ER/LA opioid analgesics are not indicated for as-needed pain relief.

The FDA is also requiring a new boxed warning on ER/LA opioid analgesics to caution that chronic maternal use of these products during pregnancy can result in neonatal opioid withdrawal syndrome.

Reference: FDA News Release, 10 September 2013 at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements

Carbamazepine: HLA-B*1502 genotype testing

Singapore — The Ministry of Health (MOH) has announced that genotyping for the HLA-B*1502 allele prior to the initiation of carbamazepine (CBZ) therapy in new patients of Asian ancestry is now considered the standard of care. These new recommendations by MOH and the Health Sciences Authority (HSA) have been made in consultation with experts in various fields such as neurology, psychiatry and dermatology, following the review of findings from local and international studies.
Confirmed PRCA cases associated with epoetin alfa accounted for 90% of total epoetin alfa-associated PRCA cases in the HSA Pharmacovigilance database since the reinstatement of the subcutaneous route for Eprex® in April 2009. This is a disproportionately high number of PRCA cases reported compared to the baseline reporting trend.

During this period, nine PRCA cases were reported from two local healthcare institutions. All cases were reported with subcutaneous use of Eprex® in chronic kidney disease patients with duration of onset ranging from seven months to 19 months.


Sunitinib malate: cutaneous reactions

Canada — A statement has been added to the product monograph indicating a potential association between sunitinib malate (Sutent®) and severe cutaneous reactions suggestive of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). If signs or symptoms are present, treatment should be discontinued. If the diagnosis of SJS or TEN is confirmed treatment must not be restarted.

Sunitinib malate is indicated for the treatment of gastrointestinal stromal tumour after failure of imatinib mesylate treatment due to resistance or intolerance. It is also indicated for the treatment of metastatic renal cell carcinoma of clear cell histology and for the treatment of patients with unresectable locally advanced or metastatic, welldifferentiated pancreatic neuroendocrine tumours, whose disease is progressive.

Epoetin alfa: increase in pure red cell aplasia

Singapore — The Health Sciences Authority (HSA) has advised of an unexpected increase in local cases of antibody-mediated pure red cell aplasia (PRCA) associated with subcutaneous administration of epoetin alfa (Eprex®) during the period 2012 and 2013.
Panitumumab: RAS status before treatment

**United Kingdom** — The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that evidence of wildtype rat sarcoma viral oncogene (RAS) status is required before initiating treatment with panitumumab (Vectibix®) alone or in combination with other chemotherapy in the treatment of metastatic colorectal cancer. Inferior progression-free survival and overall survival have been shown in patients with RAS mutations beyond KRAS exon 2 who received panitumumab combined with oxaliplatin-containing (Folfox®) chemotherapy versus Folfox® alone.

These findings emphasize that panitumumab is contraindicated in combination with oxaliplatin-based chemotherapy in patients with mutant RAS or in whom RAS status is unknown.


Fentanyl patches: colour changes to avoid exposure

**United States of America** — The Food and Drug Administration (FDA) is requiring colour changes to the writing on fentanyl (Duragesic®) pain patches in an effort to prevent accidental exposure. Used fentanyl patches require proper disposal after use.

FDA continues to learn of deaths from accidental exposure to fentanyl patches and is requiring the manufacturer to print the name and strength of the drug on the patch in long-lasting ink, in a color that is clearly visible to patients and caregivers.


Ornidazole: adverse eye effects

**New Zealand** — Since 1987, the Centre for Adverse Reactions Monitoring (CARM) has received 10 reports where the patient experienced eye problems — mainly described as visual impairment and blurred vision — following treatment with ornidazole, used to treat bacterial infections.

Visual impairment and/or blurred vision can affect the user’s ability to drive or operate machinery. Anyone experiencing these problems should not drive or operate machinery.


Statins: risk of acute kidney injury

**New Zealand** — Medsafe has identified a possible signal of acute kidney injury (without rhabdomyolysis) with the use of high-dose statins following a review of published literature. Myopathy or rhabdomyolysis is a well-known adverse effect of statin therapy, with acute kidney injury occurring secondary to these symptoms. Recent studies however have suggested that there is a risk of acute kidney injury occurring without prior or concurrent onset of myopathy or rhabdomyolysis. The overall benefit-risk balance of statins remains positive.

The Centre for Adverse Reactions Monitoring (CARM) has received a total of 38 reports which fulfil the criteria for acute kidney injury with statins. Of these, 24 also report rhabdomyolysis or creatine kinase elevations, which are suggestive of muscle problems.

Acute kidney injury is defined in different ways, from acute renal failure with tubular...
necrosis or unspecified, through to need for renal replacement therapy such as haemodialysis, peritoneal dialysis or kidney transplantation.


Low molecular weight heparin: risk of spinal column bleeding and paralysis

United States of America — The Food and Drug Administration (FDA) is recommending that health care professionals carefully consider the timing of spinal catheter placement and removal in patients taking anticoagulant drugs, such as enoxaparin, and delay dosing of anticoagulant medications for some time interval after catheter removal to decrease the risk of spinal column bleeding and subsequent paralysis after spinal injections, including epidural procedures and lumbar punctures. These new timing recommendations, which can decrease the risk of epidural or spinal hematoma, will be added to the labelling of anticoagulant drugs known as low molecular weight heparins, including Lovenox® and generic enoxaparin products and similar products.

Health care professionals and institutions involved in performing spinal/epidural anesthesia or spinal punctures should determine, as part of a pre-procedure checklist, whether a patient is receiving anticoagulants and identify the appropriate timing of enoxaparin dosing in relation to catheter placement or removal. To reduce the potential risk of bleeding, consider both the dose and the elimination half-life of the anticoagulant:

For enoxaparin, placement or removal of a spinal catheter should be delayed for at least 12 hours after administration of prophylactic doses such as those used for prevention of deep vein thrombosis. Longer delays (24 hours) are appropriate to consider for patients receiving higher therapeutic doses of enoxaparin (1 mg/kg twice daily or 1.5 mg/kg once daily).

A post-procedure dose of enoxaparin should usually be given no sooner than 4 hours after catheter removal. In all cases, a benefit-risk assessment should consider both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors.

Epidural or spinal hematomas are a known risk of enoxaparin in the setting of spinal procedures and are already described in warnings and precautions for Lovenox® and generic enoxaparin products. However, these serious adverse events continue to occur.

It is important to note that all anticoagulants carry the risk of causing spinal bleeding when used in conjunction with epidural/spinal anesthesia or spinal puncture.


Pazopanib: hepatotoxicity

Canada — Healthcare professionals have been reminded that pazopanib hydrochloride (Votrient®) is associated with hepatotoxicity including hepatic failure and fatalities.

Physicians are asked to monitor serum liver tests before initiation and during treatment. Testing of serum liver enzyme and bilirubin levels during treatment has increased in frequency and periodic monitoring should continue after month four.

Pazopanib hydrochloride is a tyrosine kinase inhibitor indicated for treatment of metastatic renal cell (clear cell) carcinoma as first-line systemic therapy or second line systemic therapy after
treatment with cytokines for metastatic disease. It is also indicated for treatment of patients with selective subtypes of advanced soft tissue sarcoma who have received prior chemotherapy for metastatic disease, or who have progressed within 12 months after (neo) adjuvant therapy.

Concomitant use of pazopanib hydrochloride and statins should be undertaken with caution and close monitoring.


Regadenoson and adenosine: fatal cardiac reactions

United States of America — The Food and Drug Administration (FDA) has warned healthcare professionals of the rare but serious risk of heart attack and death with use of the cardiac nuclear stress test agents regadenoson (Lexiscan®) and adenosine (Adenoscan®).

Patients with signs or symptoms of unstable angina or cardiovascular instability may be at greater risk for serious cardiovascular adverse reactions.

Regadenoson and adenosine are approved for use during cardiac nuclear stress tests in patients who cannot exercise adequately. They cause blood to flow preferentially to the healthier, unblocked or unobstructed arteries. In some cases, this reduced blood flow can lead to a heart attack, which can be fatal.

Cardiac resuscitation equipment and trained staff should be available before administering regadenoson or adenosine.


Thiocolchicoside: risk of aneuploidy

European Union — The European Medicines Agency’s Committee on Human Medicinal Products (CHMP) has recommended that thiocolchicoside-containing medicines for use by mouth or injection should be restricted across the European Union.

These medicines are now recommended only as an add-on treatment for painful muscle contractures resulting from spinal conditions in adults and adolescents 16 years of age or older. In addition, the dose of thiocolchicoside by mouth or injection should be restricted.

The review of thiocolchicoside was triggered by the Italian medicines regulatory agency, AIFA, following new experimental evidence which suggested that thiocolchicoside was broken down in the body into a metabolite (M2 or SL59.0955) that could damage dividing cells, resulting in aneuploidy. Aneuploidy is a risk factor for harm to the developing fetus, reduced fertility in men and in theory could increase the risk of developing cancer.

Preparations for local application to the skin, which do not produce substantial levels of M2 in the body, are not affected by this review.


Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious or unexpected adverse drug reactions. A signal is defined as “reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information”. All signals must be validated before any regulatory decision can be made.
Regulatory Action and News

Helsinki Declaration: 2013 revision

The World Medical Association (WMA) has adopted and published a revised version of the Helsinki Declaration on biomedical research involving human subjects.

Delegates at the WMA’s 64th annual Assembly in Fortaleza, Brazil, voted overwhelmingly to support the changes which provide for increased protection for vulnerable groups involved in research and include a new provision for compensating people harmed as a result of participating in research. In addition, there are expanded requirements for post-study arrangements to ensure that participants involved in research are informed of the results and have access to any beneficial treatments that emerge.

The changes agreed are all about providing a greater degree of protection for those involved in research. The revised Helsinki Declaration requires greater transparency in medical research, more accountability and increased patient safety. The changes place further obligations on research sponsors, on researchers themselves and on host governments to protect research subjects.

This is the seventh time the Helsinki Declaration has been revised since its establishment, with notes of clarification being added in 2002 and 2004. It is the most important set of international ethical regulations in biomedical research currently available and is a core document of the WMA. It was first adopted in 1964 and provides the basis for ethical principles governing medical research involving human subjects.


EudraCT: new version launched

European Union — The European Medicines Agency has launched a new version of the European Clinical Trials Database (EudraCT). This new version, EudraCT V9, marks the initial step of a process through which summary clinical trial results will be made publicly available through the EU Clinical Trials Register (EU CTR).

EudraCT is a database used by national authorities to enter protocol-related information on clinical trials submitted by clinical trial sponsors but also includes protocol-related information on clinical trials in third countries if they are included in a Paediatric Investigation Plan (PIP).

EudraCT already contains protocol-related information submitted by sponsors for interventional clinical trials conducted in European Economic Area countries and/or in third countries, when the clinical trial is part of an agreed PIP. As of today, clinical-trial sponsors are encouraged to register on the EudraCT web site to start uploading summary results. Results posted by sponsors in EudraCT will start to become publicly available once the Agency has launched the complementary new version of the EU CTR towards the end of the year. The content and level of detail of the summary results is set out in a European Commission guideline and in its technical guidance.

This initial release of EudraCT will be followed by further updates to the system in 2014 which will provide improved
functionalities for sponsors and EU regulatory authorities. With the launch of these further iterations of EudraCT by mid-2014, the modalities and timing of posting of result-related information as described in the EC guideline will apply, and sponsors will then be required to post result-related information.

The EMA supports international standardization of data requirements for clinical trial registration. The Agency will make the data descriptions and technical specifications available to enable stakeholders to build systems that can generate structured data sets and upload them electronically into EudraCT.


WHO PQP now charging application fees

World Health Organization — The WHO Prequalification of Medicines Programme (PQP) has been externally funded until now and was able to operate successfully through the generosity of donor organizations. However, PQP is no longer able to rely solely on this funding.

PQP is not moving toward a full cost recovery model but is looking to achieve a balance between external and internal funding. Over the next few years, WHO will continue to assess this balance and make adjustments as needed. Although this may appear to be a potential disincentive to manufacturers seeking prequalification of their products, fees have been set below those currently being charged by the WHO vaccines and diagnostics prequalification programmes and flexibility has been introduced whereby manufacturers who provide adequate justification may be exempted from fees or charged a reduced fee.

PQP General Guidelines for Application Fees provides more information about the fee structure for applications received on or after 1 September 2013 and is available at http://www.who.int/prequal/info_general/documents/guidelines/application_fees/PQP_application_fees_September2013.pdf


EudraGMDP database: improved information-sharing

European Union/Japan — The Japanese Ministry of Health, Labour and Welfare (MHLW) and the European Medicines Agency’s Pharmaceuticals and Medical Devices Agency (PMDA) have started entering information on good manufacturing practice (GMP) compliance related to Japanese manufacturers into the EudraGMDP database. This is the first time that information from a non-European regulator has started to be added to EudraGMDP. The initiative is expected to speed up regulatory processes and save time for importers, manufacturers and regulatory authorities.

This development is part of the mutual recognition agreement (MRA) between the European Union (EU) and Japan. It allows the European Medicines Agency (EMA), European national competent authorities and Japanese authorities to use information in EudraGMDP instead of issuing original paper GMP certificates for a number of regulatory procedures, such as marketing-authorization applications or variation applications, including the addition of a new manufacturer. The EU and Japanese regulatory authorities will now accept a reference to a EudraGMDP entry, or a downloadable file or print-out from the database, within the scope of the EU–Japan MRA.
The regulatory procedures concerned by these new measures depend on the legal frameworks in Japan and the EU, and they are clarified in relevant notices from the regulators. The EU and Japanese authorities may still request original paper GMP certificates when GMP compliance information cannot be accessed via EudraGMDP.

The EMA offers ‘read and write’ access to EudraGMDP to the regulatory authorities of all countries with which the EU has an MRA or an agreement on conformity assessment and acceptance of industrial products (ACAA). Most of these countries are already using the information in EudraGMDP for their own regulatory procedures; the Japanese authorities are the first to take the initiative to enter data into EudraGMDP.


United States of America — The Food and Drug Administration (FDA) has announced a final rule for the unique device identification system (UDI) that, once implemented, will provide a consistent way to identify medical devices. The UDI system has the potential to improve the quality of information in medical device adverse events reports, which will help the FDA identify product problems more quickly, better target recalls, and improve patient safety.

The UDI system consists of two core items. The first is a unique number assigned by the device manufacturer to the version or model of a device, called a unique device identifier. This identifier will also include production-specific information such as the product lot or batch number, expiration date, and manufacturing date when that information appears on the label.

The second component is a publicly searchable database called the Global Unique Device Identification Database (GUDID) that will serve as a reference catalogue for every device with an identifier. No identifying patient information will be stored in this device information center.

The UDI system will enhance the ability to quickly and efficiently identify marketed devices when recalled, improve the accuracy and specificity of adverse event reports and provide a foundation for a global, secure distribution chain, helping to address counterfeiting and diversion. It will also offer a clear way of documenting device use in electronic health records and clinical information systems. The UDI system is a key component of the National Medical Device PostMarket Surveillance System proposed in September 2012.

In general, high-risk medical devices (Class III) will be required to carry unique device identifiers on their label and packaging within one year and this number and corresponding device information must be submitted to the new database. Manufacturers will have three years to act for most Class II (moderate risk) devices. Manufacturers of Class I devices not exempt from UDI requirements will have five years to act.


Macitentan approved for pulmonary arterial hypertension

United States of America — The Food and Drug Administration (FDA) has approved macitentan (Opsumit®), a new adult treatment for pulmonary arterial hypertension (PAH). Macitentan is an endothelin receptor blocker.

Similar to other members of its drug class, Opsumit® carries a boxed warning
outside the body, includes disposable components and a control/monitor unit. The device works by removing certain lipoproteins from the patient’s blood. The Liposorber LA-15 System® was first approved in the United States in 1996 for lowering low density lipoprotein cholesterol in certain patients with familial hypercholesterolemia (FH).


Riociguat approved for pulmonary hypertension

United States of America — The Food and Drug Administration (FDA) has approved riociguat (Adempas®) for adult treatment of two forms of pulmonary hypertension.

Riociguat is a soluble guanylate cyclase stimulator intended for patients with chronic thromboembolic pulmonary hypertension (CTEPH) after surgery or patients who cannot undergo surgery, to improve their ability to exercise. Riociguat is also indicated for patients with pulmonary arterial hypertension (PAH) to improve their ability to exercise and to delay clinical worsening of their condition.

Adempas® carries a boxed warning alerting patients and healthcare professionals that the drug should not be used in pregnant women. Female patients can receive the drug only through the Adempas® Risk Evaluation and Mitigation Strategy (REMS) Programme. This requires that:

• Prescribers should be certified.
• All female patients should be enrolled and comply with applicable pregnancy testing and contraception requirements before initiating treatment.
• Pharmacies should be certified to dispense Adempas®.

Common side effects observed include anaemia, nasopharyngitis, sore throat, bronchitis, headache, flu and urinary tract infection.


Liposorber Apheresis System® approved for paediatric glomerulosclerosis

United States of America — The Food and Drug Administration (FDA) has approved Liposorber LA-15 System® to treat paediatric patients with primary focal segmental glomerulosclerosis (FSGS) either before transplant, or after renal transplantation in which there is recurrence of FSGS.

FSGS is a chronic kidneys disease which causes excessive loss of protein from the blood into the urine leading to nephrotic syndrome and kidney failure. A majority of children with primary FSGS will progress to end stage renal disease and will require either kidney dialysis or kidney transplant. About one quarter to one half of FSGS patients that receive a kidney transplant will have a recurrence of FSGS in their transplanted kidney.

The Liposorber LA-15 System®, a blood processing system that is used...
Common side effects observed in patients treated with riociguat included headache, dizziness, dyspepsia, peripheral edema, nausea, diarrhoea and vomiting.


Vortioxetine approved for major depressive disorder

United States of America — The Food and Drug Administration (FDA) has approved vortioxetine (Brintellix®) to treat adults with major depressive disorder.

The most common side effects reported by participants taking vortioxetine in clinical trials included nausea, constipation and vomiting. Brintellix® and other antidepressant drugs have a boxed warning and a medication guide alerting patients and healthcare professionals that antidepressants can increase the risk of suicidal thoughts and behavior in children, adolescents and young adults ages 18 to 24 during initial treatment.

Reference: FDA News Release, 30 September 2013 at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements

Pertuzumab approved as neo-adjuvant breast cancer treatment

United States of America — The Food and Drug Administration (FDA) has granted accelerated approval to pertuzumab (Perjeta®) as part of a complete treatment regimen for patients with early stage breast cancer before surgery (neo-adjuvant setting). Perjeta® was approved in 2012 for the treatment of patients with advanced or metastatic HER2-positive breast cancer.

Perjeta’s new use is intended for patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer who are at high risk of having their cancer return or metastasize, or of dying from the disease. It is to be used in combination with trastuzumab and other chemotherapy prior to surgery and may be followed by chemotherapy after surgery. Following surgery, patients should continue to receive trastuzumab to complete one year of treatment.

The confirmatory trial for this accelerated approval is being conducted in participants with HER2-positive breast cancer who had prior breast cancer surgery and are at high risk of having their cancer return. More than 4800 participants are enrolled in this trial, which will provide further data on efficacy, safety and long-term outcomes. Results are expected in 2016.

The most common side effects reported in participants receiving pertuzumab plus trastuzumab and docetaxel were hair loss, diarrhoea, nausea and a decrease in white blood cells. Other significant side effects included decreased cardiac function, infusion-related reactions, hypersensitivity reactions and anaphylaxis.

Reference: FDA News Release, 30 September 2013 at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements

Paclitaxel: expanded use for late-stage pancreatic cancer

United States of America — The Food and Drug Administration (FDA) has expanded the approved uses of paclitaxel protein-bound particles for injectable suspension, albumin-bound (Abraxane®), to treat patients with metastatic pancreatic cancer.

Abraxane® is intended for use with gemcitabine in patients with pancreatic cancer that has spread to other parts of the body.

Common side effects observed in Abraxane® plus gemcitabine treated participants include neutropaenia,
thrombocytopaenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhoea, pyrexia, vomiting, rash and dehydration. The most common serious side effects were pyrexia, dehydration, pneumonia and vomiting. Other clinically important serious side effects included sepsis and pneumonitis.

Paclitaxel was also approved to treat breast cancer in 2005 and non-small cell lung cancer in 2012.


Lipid injectable emulsion approved for parenteral nutrition

United States of America — The Food and Drug Administration (FDA) has approved lipid injectable emulsion, USP (Clinolipid®) for parenteral nutrition in adults, providing a source of calories and essential fatty acids for patients who are unable to eat or drink.

Clinolipid® is a lipid emulsion that contains a mixture of refined olive oil and refined soybean oil which should be used with caution in patients with pre-existing liver disease or liver insufficiency. Clinolipid® should not be used in patients with a known hypersensitivity to egg or soybean proteins, or in those with hyperlipidaemia.

The most common side effects in patients treated with Clinolipid® during clinical trials included infectious complications, nausea and vomiting, excess lipids in the blood, high blood sugar, low levels of protein in the blood and abnormal liver function tests.

Clinolipid® is not indicated for use in pre-term infants. The product carries a warning about the risk of death in pre-term infants after infusion of intravenous lipid emulsions. Neither is Clinolipid® indicated for use in other paediatric patients because it is not known what amount of essential fatty acids meet the nutritional needs of children.


Ibrutinib approved for mantle cell lymphoma

United States of America — The Food and Drug Administration (FDA) has approved ibrutinib (Imbruvica®) to treat patients with mantle cell lymphoma (MCL), a rare and aggressive type of blood cancer.

MCL is a rare form of non-Hodgkin lymphoma and represents about six percent of all non-Hodgkin lymphoma cases in the United States. By the time MCL is diagnosed, it usually has already spread to the lymph nodes, bone marrow and other organs.

Ibrutinib is intended for patients with MCL who have received at least one prior therapy. It works by inhibiting the enzyme needed by the cancer to multiply and spread. Imbruvica® is the third drug approved to treat MCL. Velcade® (2006) and Revlimid® (2013) are also approved to treat the disease.

The most common side effects reported in participants receiving ibrutinib are thrombocytopenia, diarrhoea, neutropenia, anemia, fatigue, musculoskeletal pain, edema, upper respiratory infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting, and decreased appetite. Other clinically significant side-effects include bleeding, infections, kidney problems and the development of other types of cancers.

Eslicarbazepine acetate approved for adult seizures

United States of America — The Food and Drug Administration (FDA) has approved eslicarbazepine acetate (Aptiom®) as an add-on medication to treat seizures associated with epilepsy.

Eslicarbazepine acetate is approved for the treatment of partial seizures, the most common type of seizure seen in people with epilepsy.

The most common side effects reported by patients receiving eslicarbazepine acetate in clinical trials included dizziness, drowsiness, nausea, headache, double-vision, vomiting, fatigue and loss of coordination. These and other side effects and recommendations for monitoring are described in the drug label.

Like other antiepileptic drugs, eslicarbazepine acetate may cause suicidal thoughts or actions in a very small number of people.


Dolutegravir approved for HIV

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended granting a marketing authorization for dolutegravir (Tivicay®) in combination with other antiretroviral medicines for the treatment of adults and adolescents over twelve years of age infected with human immunodeficiency virus (HIV).

Dolutegravir can be used in adult patients with and without resistance to the integrase class and in adolescents infected with HIV-1 without resistance to the integrase class.

Dolutegravir has demonstrated its efficacy in large scale studies covering previously untreated patients as well as patients with advanced treatment histories and resistant to multiple classes of HIV medicines. It also demonstrated a high barrier to resistance.

Dolutegravir has been recommended for marketing approval together with a risk management plan (RMP) which covers the risk of infrequent but potentially severe hypersensitivity reactions.

The EMA is currently consulting on new draft guidance for development of these medicines, taking into account changes in the therapeutic landscape.


Delamanid and para-aminosalicylic acid approved for multidrug-resistant tuberculosis

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended the authorization of delamanid (Deltyba®) and para-aminosalicylic acid (Paraaminosalicylic acid Lucane®), two treatment options for use in combination with other medicines against multidrug-resistant tuberculosis.

Multidrug-resistant tuberculosis is defined as tuberculosis caused by Mycobacterium tuberculosis that is resistant to at least isoniazid and rifampicin, which are two antituberculosis medicines used in standard treatment. Approximately 450 000 cases of multidrug-resistant tuberculosis occur globally every year, which corresponds to approximately 5% of the world’s annual burden of tuberculosis. In the European Union, tuberculosis is an orphan indication. It was estimated in 2011 to occur in 2.3 out of 10 000 people.
Deltyba®: The CHMP recommended granting a conditional marketing authorization for Deltyba® (delamanid), for the treatment of adult patients with pulmonary infections due to multidrug-resistant tuberculosis when an effective treatment regimen cannot otherwise be devised for reasons of resistance or tolerability. Additional studies on the long-term effectiveness of Deltyba® need to be conducted.

Para-aminosalicylic acid Lucane®: The Committee also recommended granting a marketing authorization for Para-aminosalicylic acid Lucane® against multidrug-resistant tuberculosis in adults and paediatric patients when an effective treatment regimen cannot otherwise be devised for reasons of resistance or tolerability.

Para-aminosalicylic acid, of which Para-aminosalicylic acid Lucane® is a new formulation, was the second medicine to be introduced for the treatment of tuberculosis, in 1946, and was part of standard-of-care treatment until the 1970s. Its use resumed in the 1990s with the emergence of multidrug-resistant tuberculosis.


Sofosbuvir approved for chronic hepatitis C

European Union — The European Medicines Agency’s Committee for Medicinal Products for Human use (CHMP) has recommended granting a marketing authorization for sofosbuvir (Sovaldi®) for use in combination with other medicinal products for the treatment of chronic hepatitis C (HCV) in adults.

Sofosbuvir is the first representative of a new class of antivirals that act as inhibitors of an essential enzyme of HCV, the NS5B ribonucleic acid polymerase. This medicine provides the first interferon-free treatment option for chronic hepatitis C.

Furthermore, when sofosbuvir is used in combination with pegylated interferon as well as ribavirin, shortened treatment duration down to 12 weeks (compared to 24–48 weeks with the current standard of care) is possible and provides high efficacy. This is of value considering the side-effect profile of interferon.

HCV infection is the most common single cause of liver transplantation in the EU. However, patients who do undergo liver transplantation due to hepatitis C have a worse prognosis than patients who do so for other reasons because recurrence of the virus in the graft is near-universal and often aggressive. For many of these patients, there are currently no approved treatment options that are likely to be effective.

In clinical trials, Sovaldi® in combination with ribavirin has shown its capacity to prevent reinfection of the graft, and thus provides a treatment option for patients with HCV infection who are on the waiting list for liver transplantation.

Recent Publications, Information and Events

WHO Good Governance for Medicines Model Framework

The World Health Report identifies ten leading causes of health system inefficiency, four of which are related to medicines: price, quality, use and waste.

In most countries, expenditure on pharmaceuticals comprises a large proportion of the health budget. Effective management and good governance in the pharmaceutical sector is therefore an essential element to improving efficiency and making a sustainable contribution to health systems strengthening and universal health coverage. Growing numbers of public health officials in ministries of health, medicines regulatory authorities and national procurement departments recognize the need for institutions and personnel to work in a more transparent and accountable environment in accordance with ethical professional practices.

Thirty-six countries are participating in the Good Governance for Medicines Programme (GGM) and are applying the principles of determining the strengths and weaknesses of a country’s pharmaceutical system and developing and applying appropriate interventions. A recent evaluation of the programme confirms the need for strong support to countries for strengthening governance in the pharmaceutical sector.

To further support country efforts, WHO has published the Good Governance for Medicines Model Framework. This guideline can be adapted according to country needs and proposes a combination of discipline-based and values-based strategies for effective, efficient, ethical, transparent and accountable management of pharmaceutical systems. The first edition of the framework was published in 2008 and since revised by experts and country representatives building on their experience of work already undertaken. The updated version is now available at www.who.int/medicines/areas/policy/goodgovernance/


Transparency of clinical trial data

In the context of on-going negotiations on the European Union Clinical Trials Regulation and the European Medicines Agency’s (EMA’s) work towards the proactive publication of clinical trial data, HAI Europe has published a policy paper Protecting citizens’ health: transparency of clinical trial data on medicines in the EU, with the objective of shaping the debate towards greater data transparency.

Many adverse drug reactions, including deaths, could have been avoided had the public known about the undisclosed effects of medicines. In addition, open access to trial data can facilitate independent re-analyses of claimed efficacy and comparison between therapies. The transparency of clinical trial data also responds to an ethical obligation. According to the Declaration of Helsinki, authors have the duty to make publicly available the results of their studies: whether positive, negative or inconclusive. The policy paper argues that increased public knowledge on the effects of medicines plays an
unquestionable role in the strengthening and protection of public health.


**Drug-resistant TB treatments: more support needed**

Médecins Sans Frontières (MSF) and the International Union Against Tuberculosis and Lung Disease have released the third edition of the drug-resistant TB drug report *DR-TB Drugs Under the Microscope*. The report covers the issues faced in accessing DR-TB drugs, including the high price of the new drug bedaquiline. A currently recommended DR-TB treatment regimen costs anywhere between US$ 3000 – 5000 per person per treatment. The treatment has awful side effects, is effective only half the time and lasts around two years — with people taking as many as 14 600 pills.

Also relaunched is the *Test me, treat me* DR-TB Manifesto which asks people to sign on to support people receiving treatment, better treatment options, and funding to scale up treatment. The manifesto can be accessed at http://www.msfaccess.org/TBmanifesto/.

MSF is one of the largest nongovernmental organizations providing DR-TB care. In 2012, MSF treated 29 000 patients for TB in 30 countries, and 1780 patients for DR-TB in 18 countries. The mission of the International Union Against Tuberculosis and Lung Disease is to bring innovation, expertise, solutions and support to address health challenges in low- and middle-income populations.


**2013 WHO Global Tuberculosis Report**

The World Health Organization has identified five priority action areas that could make a rapid difference between now and 2015 to strengthening the fight against tuberculosis (TB). The 2013 TB report calls for more attention to multidrug-resistant TB (MDR-TB) and better strategies to reach those who are being missed by the system.

The WHO-recommended actions are based on new data from almost 200 countries and territories. It documents how TB treatment has saved the lives of more than 22 million people, and how both the numbers of people ill with TB and those who died from the disease fell in 2012.

The report also identifies the challenges still ahead to help control the disease.


**International Pharmacopoeia: fourth edition**

The *International Pharmacopoeia* contains a collection of recommended procedures for the determination of pharmaceutical substances, excipients and dosage forms and is intended to serve as source material for reference or adaptation. The Third Supplement has now been added to the Fourth Edition of *The International Pharmacopoeia*.

**New, revised and withdrawn texts**

New and revised texts are introduced in the section on Supplementary information for ten monographs on pharmaceutical substances, thirty-one monographs on dosage forms, two general monographs, ten methods of analysis and six texts. A list of the new, revised and withdrawn texts is provided as an annex.
Artemisinin and its derivatives should no longer be used as monotherapy and fixed-dose combination formulations are now recommended. The 47th meeting of the Expert Committee on Specifications for Pharmaceutical Preparations therefore decided to withdraw these monographs.

**Pharmacopoeial Discussion Group (PDG) harmonized general texts**

A number of PDG texts have been adopted and include:

- Residue on ignition/sulphated ash
- Test for extractable volume for parenteral preparations
- Disintegration
- Test for particulate contamination: sub-visible particles
- Microbiological examination of non-sterile products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use
- Microbiological examination of non-sterile products: tests for specified micro-organism
- Test for sterility
- Tablet friability
- Bulk and tapped density of powders
- Bacterial endotoxins test
- Microbial examination of non-sterile products: microbial enumeration tests

**Reproductions from the European Pharmacopoeia**

The following new tests have also been published in the European Pharmacopoeia:

- Measurement of consistency by penetrometry
- Resistance to crushing of tablets

**Infrared Reference Spectra**

Many monographs in The International Pharmacopoeia include an identification test using infrared spectroscopy. Such tests usually allow comparison either with a spectrum obtained from an International Chemical Reference Substance (ICRS) or with an International Infrared Reference Spectrum (IIRS). Nine additional spectra were added.

**International Chemical Reference Spectra**

The release procedure for ICRS was revised and is included in the Supplementary information.

Complete information on the texts and access to *The International Pharmacopoeia* is available online at the WHO Medicines web site.

Consultation Documents

The International Pharmacopoeia

Dissolution testing of tablets and capsules

Draft revision for inclusion in the supplementary information section of The International Pharmacopoeia (September 2013). Please address any comments to Technologies, Standards and Norms, Essential Medicines and Health Products, World Health Organization, 1211 Geneva 27, Switzerland. Or e-mail to schmidtg@who.int. All working documents are posted for comment at http://www.who.int/medicines.

Introduction
The revision of chapter 5.5 Dissolution test for solid, oral dosage forms, as published in The International Pharmacopoeia*, was based on the internationally-harmonized dissolution test developed by the Pharmacopoeial Discussion Group (PDG) which comprises representatives from the European Pharmacopoeia, the Japanese Pharmacopoeia and the United States Pharmacopeia. The revised general method presents the Paddle and Basket methods for dissolution testing. Two other general methods contained in the PDG text, namely the Reciprocating-cylinder method and the Flow-through cell have not, so far, been adopted for The International Pharmacopoeia.

*Note from the Secretariat: It is intended to publish revised chapter 5.5 Dissolution test for solid, oral dosage forms, adopted in October 2012 at the 47th WHO Expert Committee on Specifications for Pharmaceutical Preparations, together with this text in the next supplement or edition of The International Pharmacopoeia.

It is not the intention of The International Pharmacopoeia to apply retrospectively the test conditions and acceptance criteria of the revised dissolution test or to change specifications for existing products. Table 1 lists monographs with dissolution tests, which were developed applying previous versions of chapter 5.5 and which are thus not subject to the internationally-harmonized provision. In the elaboration of new monographs and revision of individual monographs in The International Pharmacopoeia the principles of the revised test, e.g. to base acceptance criteria on “Q” values (dissolution limits), will be applied.

Table 1. Monographs on solid, oral dosage forms with dissolution test conditions and specifications elaborated before chapter 5.5 Dissolution test for solid, oral dosage forms, were revised to encompass the internationally-harmonized procedure.

Amodiaquine tablets
Artemether capsules
Artemether tablets
Artemimol tablets
Artesunate tablets
Carbamazepine tablets
Chloroquine phosphate tablets
Chloroquine sulfate tablets
Doxycycline capsules
Doxycycline tablets
Efavirenz, emtricitabine and tenofovir tablets
Emtricitabine and tenofovir tablets
Emtricitabine capsules
Erythromycin ethylsuccinate tablets
Erythromycin stearate tablets
Ethambutol hydrochloride tablets
Griseofulvin tablets
Ibuprofen tablets
Indinavir capsules
Indometacin tablets
Isoniazid tablets
Isoniazid and ethambutol hydrochloride tablets
Levonorgestrel and ethinylestradiol tablets
Lopinavir and ritonavir tablets
Metronidazole tablets
Phenoxymenthylpenicillin potassium tablets
Phenytoin sodium tablets
Pyrazinamide tablets
Quinine bisulfate tablets
Quinine sulfate tablets
Rifampicin capsules
Rifampicin tablets
Ritonavir tablets
Saquinavir tablets
Sulfadoxine and pyrimethamine tablets
Sulfamethoxazole and trimethoprim tablets
Tenofovir tablets

Objective of dissolution testing
While the ultimate objective of dissolution testing is to ensure adequate and reproducible bioavailability, the objective of the dissolution tests prescribed in the individual monographs of The International Pharmacopoeia is to obtain information about the drug-release characteristics of a particular formulation or batch of a product under standardized test conditions. Compliance with the test provides an assurance that most of the active ingredient will be dissolved in an aqueous medium within a reasonable amount of time when the preparation is subject to a mild agitation. Compliance with the dissolution test does not by itself guarantee bioavailability.

Standardized conditions and limits are considered appropriate for a pharmacopoeial test that is intended to apply to a monograph covering multisource products.

Policy of The International Pharmacopoeia
Monographs on tablet and capsule preparations listed in Table 1 include a dissolution test, either with or without further information on the test conditions. As a test method
spectrophotometry is typically employed. In case a dissolution test is prescribed an additional disintegration test is not required.

In the elaboration of new tablet and capsule monographs and revision of existing monographs decisions on dissolution and disintegration testing will be taken in agreement with the guidance given by the International Conference on Harmonisation (ICH) on the application of dissolution testing to medicinal products (see http://www.ich.org). The monograph will contain a dissolution test and/or a disintegration test. For rapidly dissolving (dissolution > 80% in 15 minutes at pH 1.2, 4.0 and 6.8) dosage forms containing active ingredients which are highly soluble throughout the physiological range (dose: solubility volume < 250 ml from pH 1.2 to 6.8), disintegration is substituted for dissolution. Disintegration is most appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution.

When the disintegration test can be substituted for the dissolution test monographs on dosage forms will specify a choice between A (dissolution test) and B (disintegration test). If the disintegration requirement is not met dissolution testing has to be performed.

**Test conditions**

Following a decision made at the 45th Expert Committee meeting a standardized dissolution test is applied to conventional-release tablet and capsule formulations containing highly soluble active ingredients (Class I and III of the Biopharmaceutics Classification System (BCS)). The following conditions for a single-time test using the Paddle method are preferred:

- dissolution medium: dissolution buffer pH 6.8;
- volume of medium: 500 ml;
- rotation speed: 75 rpm;
- sampling time: 30 min.

When test conditions are not specified in the individual monograph it is recommended to apply similar test conditions. If the Basket method is used a rotation speed of 100 rpm is recommended.

For conventional-release tablet and capsule formulations containing poorly water-soluble active ingredients (Class II and IV of the BCS). (Classification of active ingredients included in the WHO Model List of Essential Medicines is provided by WHO in *Technical Reprt Series*, No. 937, Annex 7 (2006).) decisions on the appropriate test conditions are taken on a case-to-case basis. A single-point dissolution test is normally applied. Because of the low aqueous solubility dissolution medium of volume 900 ml and addition of a surfactant may be needed. The concentration of active ingredient at 100% dissolution should not exceed approximately 35% saturation.

For delayed-release dosage forms two-stage testing according to the procedure in 5.5 Dissolution test for solid, oral dosage forms is applied. It is important to consider the population of individuals who will be taking the dosage form when designing the test, e.g. administration of the dosage form to achlorhydric patients may require testing for resistance of the product against gastric juice at elevated pH, for example, pH 3.5.
For sustained-release dosage forms the appropriate test conditions and sampling procedures are specified in the monograph. Three time-points are applied.

**Acceptance criteria**

The revised dissolution test contains acceptance criteria for conventional-release, delayed-release and sustained-release dosage forms. The acceptance criteria are identical to those stated in the internationally harmonized dissolution test. The harmonized dissolution limits (Q-values) are applied in new and revised monographs (i.e., monographs on solid, oral dosage forms containing a dissolution test, but not listed in Table 1).

The three-level acceptance criteria, i.e. S1, S2 and S3 for conventional-release dosage forms, are not applied in monographs listed in Table 1; acceptance criteria for a two-stage test (6+6 dosage units) are specified in some monographs. For dosage forms for which the monograph require compliance with 5.5 Dissolution test for solid, oral dosage forms, but without specification of test conditions, it is recommended to apply a test using Q = 75% and the three-level acceptance criteria.

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**General monograph on parenteral preparations.**

**Test for bacterial endotoxins (3.4)**

Draft for inclusion in the revised General Monograph on Parenteral Preparations in The International Pharmacopoeia (September 2013).

Please address any comments to Technologies, Standards and Norms, Essential Medicines and Health Products, World Health Organization, 1211 Geneva 27, Switzerland. Or e-mail to schmidt@who.int. All working documents are posted for comment at http://www.who.int/medicines.

During the forty-seventh meeting of the Expert Committee on Specifications for Pharmaceutical Preparations in October 2012 a revision of the general monograph on parenteral preparations was adopted.

One of the major changes to the monograph on parenteral preparations was the required compliance of all parenteral preparations with the test for bacterial endotoxins (or, where justified, pyrogens). As a consequence individual monographs on injectable dosage forms in The International Pharmacopoeia (Ph.Int.) were investigated with a view to add a limit for bacterial endotoxins to each monograph that currently does not include such a requirement.

The limits proposed are calculated using the following approaches (for details see Table 2).

- For the monograph on Ergometrine hydrogen maleate injection, the limit given in The International Pharmacopoeia for the respective pharmaceutical substance (for parenteral use) was applied to the strength of the respective dosage form listed in the WHO Model List of Essential Medicines (EML).

- For the monographs on Ephedrine sulfate injection, Magnesium sulfate injection, Oxytocin injection, Prednisolone sodium phosphate injection and Zidovudine intra-
venous infusion, the limits given in the respective monographs of the United States Pharmacopeia (USP) were taken and applied to the strength of the respective dosage forms listed in the EML.

- For the monographs on Artemether injection, Artemotil injection, Melarsoprol injection, Pentamidine isetionate powder for injections and Quinine dihydrochloride injection the endotoxin limits were calculated using recommendations given in Chapter 3.4 Test for bacterial endotoxins:

Table 1. Proposed limits for the bacterial endotoxins test for Ph.Int. monographs on parenteral preparations currently lacking such a specification

<table>
<thead>
<tr>
<th>Ph.Int. monographs on parenteral preparations currently lacking limits for the bacterial endotoxins test</th>
<th>Proposed limits for the bacterial endotoxins test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Artemether injection</td>
<td>not more than 1.56 IU of endotoxin per mg Artemether</td>
</tr>
<tr>
<td>2 Artemotil injection</td>
<td>not more than 1.04 IU of endotoxin per mg Artemotil</td>
</tr>
<tr>
<td>3 Ephedrine sulfate injection</td>
<td>not more than 85 IU of endotoxin per ml</td>
</tr>
<tr>
<td>4 Ergometrine hydrogen maleate injection</td>
<td>not more than 140 IU of endotoxin per ml</td>
</tr>
<tr>
<td>5 Melarsoprol injection</td>
<td>not more than 50 IU of endotoxin per ml</td>
</tr>
<tr>
<td>6 Magnesium sulfate injection</td>
<td>not more than 45 IU of endotoxin per ml</td>
</tr>
<tr>
<td>7 Oxytocin injection</td>
<td>not more than 357 IU of endotoxin per ml</td>
</tr>
<tr>
<td>8 Pentamidine isetionate powder for injection*</td>
<td>not more than 1.25 IU of endotoxin per mg pentamidine isetionate</td>
</tr>
<tr>
<td>9 Prednisolone sodium phosphate for injection**</td>
<td>not more than 5.0 IU of endotoxin per mg prednisolone sodium phosphate</td>
</tr>
<tr>
<td>10 Quinine dihydrochloride injection</td>
<td>not more than 300 IU of endotoxin per ml</td>
</tr>
<tr>
<td>11 Zidovudine intravenous infusion</td>
<td>not more than 10 IU of endotoxin per ml</td>
</tr>
</tbody>
</table>

* The title of the monograph should also be changed to Pentamidine isetionate for injection.  
** The title of the monograph should also be changed to Prednisolone sodium phosphate for injection.
the endotoxin limit for parenteral preparations, defined on the basis of dose, is equal to:

\[
\text{endotoxin limit} = \frac{K}{M}
\]

K = threshold pyrogenic dose of endotoxin per kilogram of body mass (i.e. 5.0 IU per kg for any route of administration other than intrathecal)

M = maximum recommended bolus dose of product per kilogram of body mass. (When the product is to be injected at frequent intervals or infused continuously, M is the maximum total dose administered in a single hour period.)

In case the EML recommends different strengths of the same medicine the endotoxin limit is specified per mg active ingredient (see Artemether injection and Artemotil injection); in case only one strength is listed the limit is defined per ml (injection solution) (see Melarsoprol injection and Quinine dihydrochloride injections). For powders for injections the endotoxin limit is given per mg of active ingredient.

Additional changes
In the new general monograph on Parenteral preparations the statement is made that:

“For powders and concentrates for injections and intravenous infusions, the amount of the preparation to be tested and the nature and volume of the liquid in which it is to be dissolved, suspended or diluted is specified in the individual monograph.”

It is proposed to delete this sentence since the preparation of the sample solution is sufficiently described in Chapter 3.4. The harmonized text requires that the samples should be dissolved or diluted in aqueous solutions so that the final solutions do not exceed the maximum valid dilution (MVD).

In the monograph on Metronidazole injection the following provision for the test for bacterial endotoxins is made:

“Carry out the test as described under 3.4 Test for bacterial endotoxins. Dilute the injection, if necessary, with water LAL to give a solution containing 5 mg per ml (solution A). Solution A contains not more than 3.5 IU of endotoxin per ml. Carry out the test using the maximum valid dilution of solution A calculated from the declared sensitivity of the lysate used in the test.”

This sentence should be changed to read:

“Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 3.5 IU of endotoxin per ml.” Same rationale applies as given above.

For endotoxin limits already specified in The International Pharmacopoeia two phrases are used:

“… not more that x IU of endotoxin per mg/ml …”

“… not more that x IU of endotoxin RS per mg/ml …”
Table 2. Data used in the calculation of bacterial endotoxin limits

<table>
<thead>
<tr>
<th>Ph.Int. monographs lacking endotoxin limit</th>
<th>Endotoxin limits in respective USP monographs</th>
<th>Info on strength of dosage form (EML or PH.INT)</th>
<th>Info on dosage and route of application</th>
<th>K (IU/kg)</th>
<th>M (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemether injection</td>
<td>No USP monograph</td>
<td>17th EML: 80 mg/ml in 1-ml ampoule (oily injection); Ph.Int.: 80 mg/ml in 1-ml ampoule (oily injection), other available strengths: 40 mg/ml (paediatric formulation), 60 mg/ml, 100 mg/ml (adult formulation).</td>
<td>Intramuscular injection For adults, artesunate 2.4 mg/kg BW IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended treatment. Artemether, or quinine, is an acceptable alternative if parenteral artesunate is not available: artemether 3.2 mg/kg BW IM given on admission then 1.6 mg/ kg BW per day*.</td>
<td>5</td>
<td>3.2</td>
</tr>
<tr>
<td>Artemotil injection</td>
<td>No USP monograph</td>
<td>Not on the 17th EML Ph. Int.: Available strengths: 50 mg/ml (paediatric formulation), 75 mg/ml, 150 mg/ml (adult formulation)</td>
<td>Artece® 150 must only be applied via IM route. 3-day treatment course Initial dose: injection of 4.8 mg artemotil per kg BW evenly divided over both anterior thighs. Follow-up doses: 1.6 mg per kg BW after 6, 24, 48 and 72 hours in alternating thighs.</td>
<td>5</td>
<td>4.8</td>
</tr>
<tr>
<td>Ephedrine sulfate injection</td>
<td>Not more than 1.7 USP Endotoxin Units per mg of ephedrine sulfate</td>
<td>Not on the 17th EML Ph. Int.: Strength 50 mg/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ergometrine hydrogen maleate injection</td>
<td>No USP monograph</td>
<td>Ph. Int.: Ergometrine hydrogen maleate for parenteral use contains not more than 700.0 IU of endotoxin RS per mg Strength in EML: 200 μg/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melarsoprol injection</td>
<td>No USP monograph</td>
<td>17th EML: Injection: 3.6% solution (180 mg in 5 ml ampoule)</td>
<td>Treatment of T. brucei rhodesiense and T. brucei gambiense with meningo encephalitic involvement (see above), by slow IV injection, ADULT and CHILD, dose gradually increased from 1.2 mg/kg to maximum of 3.6 mg/kg daily in courses of 3–4 days with intervals of 7–10 days between courses; alternatively for T. brucei gambiense infection, 2.2 mg/kg daily for 10 days.</td>
<td>5</td>
<td>3.6</td>
</tr>
<tr>
<td>Ph.Int. monographs lacking endotoxin limit</td>
<td>Endotoxin limits in respective USP monographs</td>
<td>Info on strength of dosage form (EML or PH.INT)</td>
<td>Info on dosage and route of application</td>
<td>K</td>
<td>M</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Magnesium sulfate injection</td>
<td>Not more than 0.09 USP Endotoxin Units per mg of magnesium sulfate (MgSO4·7H2O)</td>
<td>17th EML: 500 mg of magnesium sulfate hepta-hydrate per ml in 2 or 10 ml ampoule</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxytocin injection</td>
<td>Not more than 35.7 Endotoxin Units per USP Oxytocin Unit</td>
<td>17th EML: 10 IU in 1 ml.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentamidine isetionate powder for injection</td>
<td>No monograph</td>
<td>17th EML: Powder for injection: 200 mg (as isetionate) in vial.</td>
<td>Visceral leishmaniasis (unresponsive to, or intolerant of, antimonial compounds), by deep IM injection or by IV infusion, ADULT and CHILD, 4 mg/kg 3 times a week for 5–25 weeks or longer, until 2 consecutive splenic aspirates 14 days apart are negative (see page 186)</td>
<td>5 IU/kg</td>
<td>4 mg/kg</td>
</tr>
<tr>
<td>Prednisolone sodium phosphate injection</td>
<td>Not more than 5.0 IU USP Endotoxin Units per mg prednisolone phosphate</td>
<td>Not in 17th EML. Strength in 12th EML: prednisolone powder for injection, 20 mg, 25 mg (as sodium phosphate or sodium succinate) in vial.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine dihydro-chloride injection</td>
<td>No monograph</td>
<td>17th EML: Injection: 300 mg quinine hydrochloride/ml in 2 ml ampoule.</td>
<td>Treatment of multidrug-resistant P. falciparum malaria (in patients unable to take quinine by mouth), by slow IV infusion, (over 4 hours) ADULT, initially 20 mg/kg quinine dihydrochloride followed by 10 mg/kg every 8 hours; CHILD, initially 20 mg/kg quinine dihydrochloride followed by 10 mg/kg every 12 hours; initial dose should be halved in patients who have received quinine, quinidine or mefloquine during the previous 12–24 hours (see page 198)</td>
<td>5 IU/kg</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td>Zidovudine IV infusion</td>
<td>Not more than 1.0 IU of USP Endotoxin Units per mg of zidovudine</td>
<td>Strength in 17th EML: solution for IV infusion injection: 10 mg/ml in 20 ml vial</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
All expressions using “IU of endotoxin RS” should be changed to “IU of endotoxin” as it is sufficient to require that the WHO International Standard for endotoxin has to be used as a standard (or an endotoxin reference standard that has been calibrated against this standard, see 3.4 Test for bacterial endotoxins, section Preparation of standard endotoxin stock solution).

Niclosamidum
Niclosamide

Niclosamide, anhydrous
Niclosamide monohydrate

Draft revision of a monograph for inclusion in The International Pharmacopoeia (September 2013). Please address any comments to Technologies, Standards and Norms, Essential Medicines and Health Products, World Health Organization, 1211 Geneva 27, Switzerland. Or e-mail to schmidth@who.int. All working documents are posted for comment at http://www.who.int/medicines.

Note from the Secretariat. Niclosamide suffers pseudopolymorphic and polymorphic transformations when exposed to different conditions. Following investigations into these transitions by a WHO Collaborating Centre it is proposed to revise the monographs on Niclosamide and Niclosamide tablets. Deleted sections are indicated by […]

Molecular formula. $C_{13}H_8C_{12}N_2O_4$ (anhydrous); $C_{13}H_8C_{12}N_2O_4\cdot H_2O$ (monohydrate).

Relative molecular mass. 327.1 (anhydrous); 345.1 (monohydrate)

Graphic formula

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{Cl} & \quad \text{Cl} \\
\text{NO}_2 & \quad \text{nH}_2\text{O} \\
n = 0 & \quad (\text{anhydrous}) \\
n = 1 & \quad (\text{monohydrate})
\end{align*}
\]

Chemical name. 2′,5-Dichloro-4′-nitrosalicylanilide; 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide; CAS Reg. No. 50-65-7 (anhydrous). 2′,5-Dichloro-4′-nitrosalicylanilide monohydrate; 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide monohydrate; CAS Reg. No. 73360-56-2 (monohydrate).

[...]
**Additional information.** Anhydrous Niclosamide is hygroscopic. Niclosamide monohydrate may exhibit polymorphism.

[...]

**Identity tests**

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

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. For the anhydrous substance the infrared absorption spectrum is concordant with the spectrum obtained from niclosamide RS which has been dried at 100–105 °C for 4 h, or with the reference spectrum of niclosamide. For the monohydrate, dry the substance to be examined and the niclosamide RS at 100–105 °C for 4 h. The infrared absorption spectrum of the dried substance is concordant with the spectrum obtained from the dried niclosamide RS or with the reference spectrum of niclosamide. The infrared absorption spectrum is concordant with the reference spectrum of a relevant form of niclosamide.

[...]

**Niclosamidi compressi**

**Niclosamide tablets**

[...]

**Identity tests**

Heat a quantity of the powdered tablets equivalent to 0.5 g of Niclosamide with 25 ml of ethanol (~750 g/l) TS, filter while hot and evaporate to dryness on a water-bath. Dry the residue at 100–105 °C for 4 h.

The residue complies either with test A alone or with tests B, C and D.

A. Carry out the examination with the dried residue as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from niclosamide RS, which has been dried at 100–105 °C for 4 h, or with the reference spectrum of niclosamide.

[...]

**Sulfamethoxazoli et trimethoprimi infusio intraveno**

**Sulfamethoxazole and trimethoprim intravenous infusion**

Draft revision of a monograph for inclusion in The International Pharmacopoeia (July 2013). Please address any comments to Technologies, Standards and Norms, Essential Medicines and Health Products, World Health Organization, 1211 Geneva 27, Switzerland. Or e-mail to schmidth@who.int. All working documents are posted for comment at http://www.who.int/medicines.
Category. Antibacterials.

Requirements

Comply with the monograph for Parenteral preparations.

Definition. Sulfamethoxazole and Trimethoprim intravenous infusion is a sterile solution containing Trimethoprim and sodium derivative of Sulfamethoxazole. It is prepared immediately before use by diluting Sulfamethoxazole and Trimethoprim sterile concentrate according to the manufacturers’ instructions.

SULFAMETHOXAZOLE AND TRIMETHOPRIM STERILE CONCENTRATE

Description. A colourless or slightly yellow solution.

Storage: Sulfamethoxazole and Trimethoprim sterile concentrate should be kept in tightly-closed, single-dose, light-resistant glass-containers.

Additional information. Strengths in the current WHO Model List of Essential Medicines: 80 mg per ml Sulfamethoxazole, 16 mg per ml Trimethoprim in 5 ml or 10 ml ampoule. Strengths in the current WHO Model List of Essential Medicines for Children: 80 mg per ml Sulfamethoxazole, 16 mg per ml Trimethoprim in 5 ml or 10 ml ampoule.

Requirements

Comply with the monograph for Parenteral preparations.

Definition. Sulfamethoxazole and Trimethoprim sterile concentrate is a sterile solution containing Trimethoprim and the sodium derivative of Sulfamethoxazole. It contains not less than 90.0% and not more than 110.0% of the amounts of Sulfamethoxazole (C₁₀H₁₁N₃O₃S) and Trimethoprim (C₁₄H₁₈N₄O₃) stated on the label.

Identity tests

Either tests A or D together with E and F, or tests B and C may be applied.

A. Carry out test A.1 or, where UV detection is not available, test A.2.

A.1 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 100 volumes of dichloromethane R, 10 volumes of methanol R and 5 volumes of dimethylformamide R as the mobile phase. Apply separately to the plate 5 µl of each of the following two solutions in methanol R. For solution (A) evaporate to dryness on a steam bath a volume of the concentrate, containing about 0.16 g of Sulfamethoxazole, shake the residue with 8 ml of methanol R and filter. For solution (B) use 20 mg of sulfamethoxazole RS and 4 mg of trimethoprim RS per ml. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air or in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spots obtained with solution (A) correspond in position, appearance and intensity to those obtained with solution (B).
A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and the conditions described above under test A.1. Spray the plate with potassium iodobismuthate TS2 solution.

The principal spots obtained with solution (A) correspond in position, appearance and intensity to those obtained with solution (B).

B. Add drop-wise to 75 ml of hydrochloric acid (~3.65 g/l) TS a volume of the concentrate containing about 0.8 g of Sulfamethoxazole, stirring continuously. Allow the suspension to stand for 5 minutes and filter through a sintered-glass filter. Wash the residue with 10 ml of water R, recrystallize from ethanol (~750 g/l) TS and dry at 105 °C. Dissolve the residue in a minimum volume of sodium carbonate (~50 g/l) TS, add hydrochloric acid (~36.5 g/l) TS drop-wise until precipitation is complete, filter, wash the residue sparingly with water R and dry at 105 °C. Carry out the test as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum of the residue is concordant with the spectrum obtained from sulfamethoxazole RS or with the reference spectrum of sulfamethoxazole.

C. To a volume of the concentrate containing about 80 mg of Trimethoprim add 30 ml of sodium hydroxide (~4 g/l) TS and extract with two quantities, each of 50 ml, of dichloromethane R. Wash the combined extracts with two quantities, each of 10 ml, of sodium hydroxide (~4 g/l) TS and then with 10 ml of water R. Shake with 5 g of anhydrous sodium sulfate R, filter and evaporate the filtrate to dryness. Carry out the test as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum of the residue is concordant with the spectrum obtained from trimethoprim RS or with the reference spectrum of trimethoprim.

D. See the test described under Assay method A. The retention times of two principal peaks in the chromatogram obtained with solution (1) correspond to those in the chromatogram obtained with solution (2).

E. Dilute a volume of concentrate containing about 80 mg of sulfamethoxazole to 10 ml with water R. Add 1 ml of sodium hydroxide (~4 g/l) TS and 3 ml of 1% copper sulphate (~10g/l) TS drop by drop, until the colour change is complete. Green precipitates are produced.

F. Evaporate a volume of concentrate containing 32 mg of trimethoprim to dryness on a water bath. To the residue, add a drop of ammonium vanadate TS, a dark brown colour is produced.

**pH value (1.13).** pH of the solution, 9.5–11.0

**Bacterial endotoxins.** Carry out the test described under 3.4 Test for bacterial endotoxins, contains not more than 6 IU of endotoxin per mg Sulfamethoxazole.

**Related substances**

**Trimethoprim-related substances**

Carry out the test as described under 1.14.1. Thin-layer chromatography, using silica gel R4 as the coating substance and a mixture of 97 volumes of chloroform R, 7.5 volumes of methanol R and 1 volume of ammonia (~260 g/l) TS as the mobile
Apply separately to the plate 10 µl of each of the following three solutions. For solution (A) transfer an accurately measured volume of the concentrate, containing about 48 mg of Trimethoprim, to a glass-stoppered, 50 ml centrifuge tube. Add 15 ml of hydrochloric acid (~2.19 g/l) TS and mix. Add 15 ml of dichloromethane R, shake for 30 seconds and centrifuge for 3 minutes. Transfer the supernatant layer to a 125 ml separator. Extract the dichloromethane layer in the centrifuge tube with 15 ml of hydrochloric acid (~2.19 g/l) TS, centrifuge and add the aqueous layer to the separator. Add 2 ml of sodium hydroxide (~100 g/l) TS to the solution in the separator and extract with three 20 ml portions of dichloromethane R, collecting the organic layer in a 125 ml conical flask. Evaporate the dichloromethane under a stream of nitrogen to dryness. Dissolve the residue in 1.0 ml of a mixture of equal volumes of dichloromethane R and methanol R (solvent mixture). For solution (B) use 48 mg of trimethoprim RS per ml solvent mixture. For solution (C) dilute an accurately measured volume of solution (B) with the solvent mixture to obtain a solution of 240 µg of trimethoprim RS per ml. After removing the plate from the chromatographic chamber allow it dry in air, spray with ferric chloride/potassium ferricyanide TS1 and examine the chromatogram in ultraviolet light (254 nm).

Trimethoprim and related substances have the following Rf values: trimethoprim about 0.5; and the trimethoprim degradation product about 0.6–0.7. In the chromatogram obtained with solution (A) any spot corresponding to the trimethoprim degradation product is not greater in size and intensity than the spot obtained with solution (C) (0.5%). Disregard any spots due to concentrate excipients at about Rf 0.1.

**Sulfamethoxazole related substances**

Either test A or test B may be applied.

A. Carry out the test as described under 1.14.1. Thin-layer chromatography, using silica gel R5 as the coating substance. As the mobile phase use a mixture of 25 volumes of ethanol/methanol (95/5) TS, 25 volumes of heptane R, 25 volumes of dichloromethane R and 7 volumes of glacial acetic acid R. Apply separately to the plate 10 µl of each of the following five solutions. For solution (A) transfer an accurately measured volume of the concentrate, containing about 160 mg of Sulfamethoxazole, to an evaporating dish. Evaporate the sample to dryness using a steam bath. Reconstitute the residue with 16 ml of ammonia/ethanol/methanol (1/95/5) TS. For solution (B) use 10 mg of sulfamethoxazole RS per ml ammonia/ethanol/methanol (1/95/5) TS. For solution (C) use 0.05 mg of sulfanilamide R per ml ammonia/ethanol/methanol (1/95/5) TS. For solution (D) use 0.03 mg of sulfanilic acid R per ml ammonia/ethanol/methanol (1/95/5) TS. For solution (E) dissolve 10 mg of sulfamethoxazole RS in 1.0 ml of a solution containing 0.05 mg of sulfanilamide R and 0.03 mg of sulfanilic acid R per ml of ammonia/ethanol/methanol (1/95/5) TS. After removing the plate from the chromatographic chamber allow it dry in air, spray with 4-dimethylaminobenzaldehyde TS7, allow the plate to stand for 15 minutes and examine the chromatogram.

In the chromatogram obtained with solution (A) any spot corresponding to sulfanilamide is not greater in size or intensity than the spot obtained with solution (C) (0.5%) and any spot corresponding to sulfanilic acid is not greater in size or intensity than the spot obtained with solution (D) (0.3%). The test is not valid unless the chromatogram obtained with solution (E) shows three clearly separated principal spots.
B. Carry out the test described under 1.14.4 High performance liquid chromatography, using the conditions given below under Assay method A.

Prepare the following solutions. For solution (1) transfer 1.0 ml of the concentrate containing 80 mg of Sulfamethoxazole into a test tube. Add 7 ml of the mobile phase and mix. Transfer 5.0 ml of this solution to a 100 ml volumetric flask, dilute with the mobile phase to volume, mix and filter. For solution (2) prepare 5 mg/ml of sulfanilamide R in ammonia/methanol (10/90) TS. Dilute 5.0 ml of this solution to 50.0 ml with the mobile phase. For solution (3) prepare 3 mg/ml of sulfanilic acid R in ammonia/methanol (10/90) TS. Dilute 5.0 ml of this solution to 50.0 ml with mobile phase. For solution (4) transfer 1.0 ml of each of solution (2) and (3) into a 200 ml volumetric flask and make up to volume with mobile phase. For solution (5) accurately weigh 50 mg of sulfamethoxazole RS in a 100 ml volumetric flask and dilute with solution (4) to volume.

Inject separately 20 µl each of solutions (1), (4) and (5) and record the chromatogram for 1.5 times the retention time of sulfamethoxazole.

In the chromatogram obtained with solution (5) the three principal peaks are eluted at the following relative retention times with reference to sulfamethoxazole (retention time about 11 minutes): sulfanilic acid about 0.2; sulfanilamide about 0.3. The test is not valid unless for solution (5) the resolution factor between the peaks due to sulfanilic acid and to sulfanilamide is at least 5.0 and the resolution factor between the peaks due to sulfanilamide and sulfamethoxazole is at least 10.

Measure the areas of the peak responses obtained in the chromatograms from solution (1) and (4). In the chromatogram obtained with solution (1): the area of any peak corresponding to sulfanilic acid is not more than the area of the peak due to sulfanilic acid in the chromatogram obtained with solution (4) (0.3%), and the area of any peak corresponding to sulfanilamide is not greater than the area of the peak due to sulfanilamide in the chromatogram obtained with solution (4) (0.5%).

**Assay**

Either method A or methods B and C may be applied.

A. 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 particles of base-deactivated silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm). (Hypersil BDS C18 has been found suitable). As the mobile phase use a solution prepared as follows: mix 1400 ml of water R, 400 ml of acetonitrile R and 2.0 ml of triethylamine R in a 2000 ml volumetric flask. Allow to equilibrate to room temperature and adjust with acetic acid (~10 g/l) TS to pH 5.9. Dilute to volume with water R and filter.

Prepare the following solutions. For solution (1) transfer an accurately measured volume of the concentrate containing about 80 mg of Sulfamethoxazole into a 50 ml volumetric flask. Add methanol R to volume and mix. Transfer 5.0 ml of this solution to a 50 ml volumetric flask, dilute with the mobile phase to volume, mix and filter. For solution (2) prepare a solution of 0.32 mg of trimethoprim RS and 1.60 mg of sulfamethoxazole RS per ml methanol R. Dilute 5.0 ml of this solution to 50.0 ml with the mobile phase.
Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Inject separately 20 µl each of solutions (1) and (2) and record the chromatogram for 1.5 times the retention time of sulfamethoxazole. In the chromatogram obtained with solution (2) the two principal peaks elute in the order: Trimethoprim (retention time about 6 minutes); Sulfamethoxazole (retention time about 11 minutes). The test is not valid unless the resolution factor between the peaks due to sulfamethoxazole and to trimethoprim is at least 5.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the content of Sulfamethoxazole (C₁₀H₁₁N₃O₃S) and Trimethoprim (C₁₄H₁₈N₄O₃) in the concentrate, using the declared content of C₁₀H₁₁N₃O₃S and C₁₄H₁₈N₄O₃ in sulfamethoxazole RS and trimethoprim RS.

B. To an accurately measured volume of the concentrate, containing about 48 mg of Trimethoprim, add 30 ml of sodium hydroxide (~4 g/l) TS and extract with four quantities, each of 50 ml, of dichloromethane R, washing each extract twice with a quantity of 10 ml of sodium hydroxide (~4g/l) TS. Combine the dichloromethane extracts and extract with four quantities of 50 ml of acetic acid (~60 g/l) TS. Wash the combined aqueous extracts with 5 ml of dichloromethane R and dilute to 250.0 ml with acetic acid (~60 g/l). To 10.0 ml of this solution add 10 ml of acetic acid (~60 g/l) and dilute to 100.0 ml with water R. Measure the absorbance of the resulting solution at the maximum at 271 nm.

Calculate the amount of Trimethoprim (C₁₄H₁₈N₄O₃) using the absorptivity value of 20.4
\[ A_{1\%1cm} = 204 \]

C. To an accurately measured volume of the concentrate containing about 0.4 g of Sulfamethoxazole add 60 ml of water R and 10 ml of hydrochloric acid (~420 g/l) TS. Add 3 g of potassium bromide R, cool in ice and titrate slowly with sodium nitrite (0.1 mol/l) VS, stirring constantly and determining the end-point potentiometrically.

Each ml of sodium nitrite (0.1 mol/l) VS is equivalent to 25.33 mg of Sulfamethoxazole (C₁₀H₁₁N₃O₃S).

**New reagents needed to be added to Ph.Int.:**

**Ethanol/methanol (95/5) TS**
Procedure. To 5 ml of methanol R add 95 ml of dehydrated ethanol R.

**Ammonia/ethanol/methanol (1/95/5) TS**
Procedure. To 1 ml of ammonia (~206 g/l) TS add 99 ml of Ethanol / methanol (95/5) TS.

**Ammonia/methanol (10/90) TS**
Procedure. To 10 ml of ammonia (~206 g/l) TS add 90 ml of methanol R.

**Acetic acid (~10 g/l) TS**
Acetic acid (~300 g/l) TS, diluted with water to contain about 10 g of C₂H₄O per litre.
Hydrochloric acid (~3.65 g/l) TS
Hydrochloric acid (~250 g/l) TS, dilute with water to contain 3.65 g of HCl in 1000 ml.

Hydrochloric acid (~2.19 g/l) TS
Hydrochloric acid (~250 g/l) TS, dilute with water to contain 2.19 g of HCl in 1000 ml.

Hydrochloric acid (~36.5 g/l) TS
Hydrochloric acid (~250 g/l) TS, dilute with water to contain 36.5 g of HCl in 1000 ml.

Sodium hydroxide (~4 g/l) TS
A solution of sodium hydroxide R containing about 4 g/l of NaOH (approximately 0.1 mol/l).

Sodium hydroxide (~100 g/l) TS
A solution of sodium hydroxide R containing about 100 g/l of NaOH (approximately 2.5 mol/l).

Ferric chloride/potassium ferricyanide TS1
Procedure. Dissolve 2 g of ferric chloride R and 0.5 g of potassium ferricyanide R in sufficient water to produce 20 ml.

Note. Ferric chloride/potassium ferricyanide TS2 must be freshly prepared.

4-Dimethylaminobenzaldehyde TS7
Dissolve 0.1 g of 4-dimethylaminobenzaldehyde R in 1 ml of hydrochloric acid (~420 g/l) TS, dilute with ethanol (~750 g/l) to produce 100 ml.

Ammonium vanadate TS
Dissolve 0.5 g of Ammonium vanadate in 1.5 ml water and dilute to 100 ml with sulfuric acid.

Copper(II) Sulfate (10 g/L) TS
A solution of Copper(II) sulfate R containing 10 g of CuSO4 per litre.

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**Medroxyprogesterone acetate**

Draft revision of a monograph for inclusion in The International Pharmacopoeia (September 2013). Please address any comments to Technologies, Standards and Norms, Essential Medicines and Health Products, World Health Organization, 1211 Geneva 27, Switzerland. Or e-mail to schmith@who.int. All working documents are posted for comment at http://www.who.int/medicines.
C\textsubscript{24}H\textsubscript{34}O\textsubscript{4}

**Relative molecular mass.** 386.5

**Chemical name.** 17-Hydroxy-6\textalpha{}-methylpregn-4-ene-3,20-dione acetate; 17-(acetyloxy)-6\textalpha{}-methylpregn-4-ene-3,20-dione; CAS Reg. No. 71-58-9.

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

**Solubility.** Practically insoluble in water; soluble in acetone R and dioxan R; slightly soluble in ethanol (~750 g/l) TS, methanol R and ether R.

**Category.** Progestogen.

**Storage.** Medroxyprogesterone acetate should be kept in a tight container, protected from light.

**Requirements**

**Definition.** Medroxyprogesterone acetate contains not less than 97.0% and not more than the equivalent of 103.0% of C\textsubscript{24}H\textsubscript{34}O\textsubscript{4}, calculated with reference to the dried substance.

**Identity tests**

Either tests A and C or test 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 medroxyprogesterone acetate RS or with the reference spectrum of medroxyprogesterone acetate.

B. Carry out test B.1 or, where UV detection is not available, test B.2.

B.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica R5 as the coating substance and a mixture of 10 volumes of dichloromethane R and 1 volume of ethyl acetate R as the mobile phase. Apply separately to the plate 10 μl of each of the following three solutions in dichloromethane R. For solution (A) use 5 mg of Medroxyprogesterone acetate per ml. For solution (B) use 5 mg of medroxyprogesterone acetate RS per ml. For solution (C) use 5 mg of medroxyprogesterone acetate RS and 0.2 mg of medroxyprogesterone acetate impurity F RS per ml. After removing the plate from the chromatographic chamber, heat it at 120 °C for 30 minutes, spray with 4-toluenesulfonic acid/ethanol TS and heat further at 120 °C for 10 minutes. Allow the plate to cool and examine the chromatogram in ultraviolet light (365 nm). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).
B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described under test B.1, but spray the plate with a mixture of equal volumes of sulfuric acid R and ethanol (~750 g/l) TS and heat further at 120 °C for 10 minutes. Allow the plate to cool and examine the chromatogram in daylight. The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

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

C. Use 20 mg; it yields the reaction described under 2.1 General identification tests as characteristic of acetylated substances.

**Specific optical rotation.** Use a 10 mg/ml solution in acetone R; \([\alpha]^{20} = +47°\) to +53°.

**Sulfated ash.** Not more than 1.0 mg/g.

**Loss on drying.** Dry at 105 °C for 3 hours; it loses not more than 10 mg/g.

**Impurity F**

Either method A or method B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (10 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3 µm). (Welch Ultimate XB-C18 has been found suitable).

As the mobile phase, use a solution prepared as follows: mix 44 volumes of water R and 56 volumes of acetonitrile R.

For solution (1) dissolve 20 mg of Medroxyprogesterone acetate in 5.0 ml of acetonitrile R and dilute to 10.0 ml with water R. For solution (2) use 0.01 mg of medroxyprogesterone acetate impurity F RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 200 nm.

Inject 25 µl of solution (1) and (2). In the chromatogram obtained with solution (2), impurity F is eluted at a relative retention of about 1.8 with reference to medroxyprogesterone acetate (retention time about 8 minutes).

In the chromatogram obtained with solution (1), the area of any peak corresponding to impurity F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

B. Carry out the test as described under 1.14.1. Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 10 volumes of tetrahydrofuran R, 45 volumes of tert-butyl methyl ether R and 45 volumes of heptane R as the mobile phase.
Apply separately to the plate 10 l of each of the following two solutions in dichloromethane R. For solution (A) use 20 mg of Medroxyprogesterone acetate per ml. For solution (B) use 20 mg of medroxyprogesterone acetate RS and 0.1 mg of medroxyprogesterone acetate impurity F RS per ml.

Develop the plate for a distance of about 10 cm. Allow it to dry in air and carry out a second development in the same direction using a freshly prepared mobile phase. After removing the plate from the chromatographic chamber, heat it at 100 °C to 105 °C for 30 minutes and spray with 4-toluenesulfonic acid/ethanol TS. Heat again at 120 °C for 10 minutes, allow to cool and examine the chromatogram in ultraviolet light (365 nm).

In the chromatogram obtained with solution (B) impurity F has a Rf value of about 0.78 and medroxyprogesterone acetate a Rf value of about 0.70. The test is not valid unless the chromatogram obtained with solution (B) shows two clearly separated spots. In the chromatogram obtained with solution (A) any spot due to impurity F is not more intense than the corresponding spot in the chromatogram obtained with solution (B) (0.5%).

**Related substances.** Prepare fresh solutions and perform the tests without delay.

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm). (Altima C18 has been found suitable.)

Maintain the column temperature at 45 °C.

As the mobile phase, use a solution prepared as follows: mix 15 volumes of tetrahydrofuran R, 23 volumes of acetonitrile R and 65 volumes of water R and filter.

Prepare the following solutions in the dissolution solvent prepared in mixing equal volumes of acetonitrile R and water R.

For solution (1) dissolve 20 mg of Medroxyprogesterone acetate in the dissolution solvent and dilute to 10.0 ml with the solvent mixture. For solution (2) dilute 1.0 ml of solution (1) to 100.0 ml with the solvent mixture. For solution (3) dilute 1.0 ml of solution (2) to 10.0 ml with the solvent mixture. For solution (4) use 2 mg of medroxyprogesterone acetate RS and 0.01 mg of medroxyprogesterone acetate impurity G RS per ml.

Operate with a flow rate of 1.5 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Inject separately 20 µl of solution (1), (2), (3) and (4). Record the chromatogram for about twice the retention time of medroxyprogesterone acetate in solution (2).

The following peaks are eluted at the following relative retention with reference to the peak of medroxyprogesterone acetate (retention time about 27 minutes): impurity A about 0.3; impurity I about 0.5; impurity H about 0.65; impurity B about 0.7; impurity C about 0.8; impurity G about 0.85; impurity D about 0.9; impurity E about 0.95. The test is not valid unless in the chromatogram obtained with solution (4) the resolution factor between the peaks due to impurity G and due to medroxyprogesterone acetate is at least 3.3.
In the chromatogram obtained with solution (1):

- The area of any peak corresponding to impurity D is not greater than the area of the principal peak obtained with solution (2) (1.0%);
- The area of any peak corresponding to impurity B is not greater than 0.7 times the area of the principal peak obtained with solution (2) (0.7%);
- The area of any peak corresponding to impurity A, when multiplied by a correction factor of 1.5, is not greater than 3 times of the area of the principal peak obtained with solution (3) (0.3%);
- The area of any peak corresponding to impurity G, when multiplied by a correction factor of 2.6, is not greater than 2 times of the area of the principal peak obtained with solution (3) (0.2%);
- The area of any peak corresponding to impurity C, E or I is not greater than 2 times the area of the principal peak obtained with solution (3) (0.2%);
- The area of any other impurity peak is not greater than the area of the principal peak obtained with solution (3) (0.1%);
- The sum of the areas (corrected, where necessary) of all the peaks, other than the principal peak, is not greater than 1.5 times the area of the principal peak obtained with solution (2) (1.5%). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (3) (0.05%).

**Assay**

Dissolve about 0.1 g, accurately weighed, in ethanol (~750g/l) TS to produce 100 ml; dilute 1.0 ml of this solution to 100 ml with the same solvent.

Measure the absorbance of the diluted solution in a 1 cm layer at the maximum at about 241 nm and calculate the content of C_{24}H_{34}O_{4} using the absorptivity value of 42.6 $$A_{1\%\ 1\text{cm}} = 426$$

**Impurities**

![Chemical Structure](image)

A. R1=OH, R2= CH3, R3=CO-CH3; 6-hydroxy-6-methyl-3,20-dioxopregn-4-en-17-yl acetate (6-hydroxymedroxyprogesterone acetate),
B. R1=R2=H, R2=CH3; 17-hydroxy-6-methylpregn-4-ene-3,20-dione (medroxyprogesterone),

C. 6,17a-dimethyl-3,17-dioxo-D-homoandrost-4-en-17a-yl acetate,

D. R1=CH3, R2=H, R3=CO-CH3; 6-methyl-3,20-dioxopregn-4-en-17-yl acetate (6-epimedroxyprogesterone acetate),

E. R1+R2=CH2, R3=CO-CH3; 6-methylidene-3,20-dioxopregn-4-en-17-yl acetate (6-methylenehydroxyprogesterone acetate),

F. 6-methyl-3,20-dioxo-5-pregnan-17-yl acetate (4,5-dihydromedroxyprogesterone acetate),

G. 6-methyl-3,20-dioxopregna-4,6-dien-17-yl acetate (megestrol acetate),
H. R1=R2=H, R3=CO-CH3; 3,20-dioxopregn-4-en-17-yl acetate (hydroxyprogesterone acetate)

I. (17ab)-17a-hydroxy-6,17a-dimethyl-D-homoandrost-4-ene-3,17-dione.

Reference substances to be established
medroxyprogesterone acetate RS
medroxyprogesterone acetate impurity F RS
medroxyprogesterone acetate impurity G RS

Fluconazoli
Fluconazole

Draft revision of a monograph for inclusion in The International Pharmacopoeia (July 2013). Please address any comments to Technologies, Standards and Norms, Essential Medicines and Health Products, World Health Organization, 1211 Geneva 27, Switzerland. Or e-mail to schmidth@who.int. All working documents are posted for comment at http://www.who.int/medicines.

C_{13}H_{12}F_{2}N_{6}O

Relative molecular mass. 306.3

Chemical name. 2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol; CAS Reg. No.86386-73-4.
Description. A white or almost white, crystalline powder.

Solubility. Slightly soluble in water, freely soluble in methanol, soluble in acetone.

Category. Antifungal.

Storage. Fluconazole should be kept in a tightly closed container, stored below 30 °C.

Additional information. Fluconazole is hygroscopic and exhibits polymorphism.

Requirements

Definition. Fluconazole contains not less than 99.0% and not more than 101.0% of C₁₃H₁₂F₂N₆O, calculated with reference to the dried substance.

Identity tests

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

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from fluconazole RS or with the reference spectrum of fluconazole. If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and fluconazole RS in a small amount of dichloromethane R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from fluconazole RS.

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 80 volumes of dichloromethane R, 20 volumes of methanol R, and 1 volume of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 μl of each of the following three solutions in methanol R. For solution (A) use 10 mg of Fluconazole per ml. For solution (B) use 10 mg of fluconazole RS per ml. For solution (C) use a solution containing 10 mg of fluconazole RS per ml and 1 mg of fluconazole impurity C RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in a current of air and 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). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

C. The absorption spectrum (1.6) of a 200 μg/ml solution in ethanol R, when observed between 230 nm and 300 nm, exhibits maxima at about 261 nm and 267 nm and a minimum at about 264 nm; the ratio of the absorbance of a 1 cm layer at the maximum at about 261 nm to that at the minimum at about 264 is about 1.4.

Clarity and colour of solution. A solution of 1.0 g in 20 ml of methanol R is clear and colourless.

Heavy metals

Either test A or test B may be applied.
A. 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; not more than 10 μg/g.

B. Use 1.0 g for the preparation of the test solution in methanol as described under 2.2.3 Limit test for heavy metals, Procedure 2; determine the heavy metals content according to Method A; not more than 10 μg/g.

**Sulfated ash (2.3).** Not more than 1.0 mg/g, using Method B and a platinum crucible.

**Loss on drying.** Dry to constant weight at 105 °C; it loses not more than 5 mg/g.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecysilyl groups (5 μm) (Capcell Pak® C18 MGII (4.6 x 250 mm, 5µm) has been found suitable.) As the mobile phase, use a mixture of 86 volumes of a (0.63 g/l) solution of ammonium formate R and 14 volumes of acetonitrile R.

Prepare the following solutions in the mobile phase. For solution (1) use 10 mg of Fluconazole per ml. For solution (2) dilute 5 ml of solution (1) to 100 ml, then dilute 1 ml of this solution to 10 ml. For solution (3) use 0.1 mg of fluconazole impurity C RS per ml. For solution (4), transfer 1.0 ml of solution (3) to a 10 ml volumetric flask, add 1.0 ml of solution (1) and make up to volume.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 260 nm.

Inject separately 20 μl each of solutions (1), (2), (3) and (4). Record the chromatograms for about 3.5 times the retention time of fluconazole.

The peaks are eluted at the following relative retentions with reference to fluconazole (retention time about 11 minutes): impurity B about 0.4; impurity A about 0.5; impurity C about 0.8.

The test is not valid, unless in the chromatogram obtained with solution (4) the resolution between the peaks due to impurity C and fluconazole is at least 3.0.

In the chromatogram obtained with solution (1),

- The area of any peak corresponding to impurity A is not not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4 %),

- The area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.5 is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3 %),

- The area of any peak corresponding to impurity C is not is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1 %),
• The area of any other peak, other than the principal peak, is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1 %).

• The sum of 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 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6 %). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05 %).

**Assay**

Dissolve about 0.1 g, accurately weighed, in 50 ml of anhydrous acetic acid R and titrate with perchloric acid (0.1 mol/l) VS as described under 2.6 Non-aqueous titration, Method A, determining the end-point potentiometrically.

Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 15.32 mg of $\text{C}_{13}\text{H}_{12}\text{F}_{2}\text{N}_{6}\text{O}$.

**Impurities**

\[ \text{and enantiomer} \]

A. (2RS)-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-3-(4H-1,2,4-triazol-4-yl) propan-2-ol,

B. 2-[2-fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol,

C. 1,1’-(1,3-phenylene)di-1H-1,2,4-triazole,
D. 2-(4-fluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol,

E. 1-[(6RS)-4,6-difluoro-6-(1H-1,2,4-triazol-1-yl)cyclohexa-1,4-dienyl]ethanone,

F. R=OH:(2RS)-2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl) propan-2-diol,
H. R=Br:(2RS)-1-bromo-2-(2,4-difluorophenyl)-3-(1H-1,2,4-triazol-1-yl) propan-2-ol,

G.[3-[[2RS)-2-(2,4-difluorophenyl)oxiran-2-yl]methyl]1H-1,2,4-triazol-1-yl}] methanesulfonic acid,
I. 4-amino-1-[(2RS)-2-(2,4-difluorophenyl)-2-hydroxy-3(1H-1,2,4-triazol-1-yl)propyl]-4H-1,2,4-triazolium.

[Note from Secretariat: chemical names and structures to be confirmed.]

Reference substances to be established:

Fluconazole RS
Fluconazole impurity C RS

Fluconazoli capsulae
Fluconazole capsules

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Category. Antifungal.

Storage. Fluconazole capsules should be kept in a tightly closed container and stored at a temperature not exceeding 30 °C.


Requirements

Comply with the monograph for «Capsules».

Definition. Fluconazole capsules contain Fluconazole. They contain not less than 90.0% and not more than 110.0% of the amount of fluconazole (C_{13}H_{12}F_{2}N_{6}O) stated on the label.

Identity tests

Either tests A and C or tests B and C may be applied.
A. 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 80 volumes of dichloromethane R, 20 volumes of methanol R, and 1 volume of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 10 μl of each of the following three solutions in methanol R. For solution (A) shake a quantity of the mixed contents of the capsules, containing about 100 mg of Fluconazole, with 10 ml of methanol R, filter, and use the clear filtrate. For solution (B) use 10 mg of fluconazole RS per ml. For solution (C) use a mixture of 10 mg of fluconazole RS and 10 mg of fluconazole impurity C RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in a current of air, and 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). The test is not valid, unless the chromatogram obtained with solution (C) shows two clearly separated spots.

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay method B. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

C. To a quantity of the capsule content, containing 2 mg of Fluconazole, add 10 ml of ethanol R, shake and filter. The absorption spectrum (1.6) of the resulting solution, when observed between 230 nm and 300 nm, exhibits maxima at 261 nm and 267 nm and a minimum at about 264 nm. The ratio of the absorbance of a 1 cm layer at the maximum at about 261 nm to that at the minimum at about 264 is about 1.4.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay method B. Prepare the following solutions in the mobile phase. For solution (1) use an amount of the mixed contents of 20 capsules to produce a solution containing 10 mg of Fluconazole per ml and filter the solution. For solution (2) dilute 5 volumes of solution (1) to 100 volumes, then dilute 1 volume of this solution to 10 volumes. For solution (3) use 0.1 mg of fluconazole impurity C RS per ml. For solution (4), transfer 1.0 ml of solution (3) to a 10 ml volumetric flask, add 1.0 ml of solution (1) and make up to volume.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 260 nm.

Inject separately 20 μl each of solutions (1), (2), (3) and (4). Record the chromatograms for about 3.5 times the retention time of fluconazole.

The peaks are eluted at the following relative retentions with reference to fluconazole (retention time about 11 minutes): impurity B about 0.4; impurity A about 0.5; impurity C about 0.8.

The test is not valid, unless in the chromatogram obtained with solution (4), the resolution between the peaks due to impurity C and to fluconazole is at least 3.0.
• The area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

• The area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.5 is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

• The area of any peak corresponding to impurity C is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

• The area of any other impurity peak, other than the principal peak, is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%),

• The sum of the corrected area of any peak corresponding to impurity B and the areas of all peaks, other than the peak due to fluconazole, is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Dissolution test
Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 500 ml of hydrochloric acid (~4 g/l) TS, rotating the basket at 100 revolutions per minute. At 45 minutes withdraw a sample of about 10 ml of the medium through a suitable 0.45 μm filter. Measure the absorbance (1.6) of a 1 cm layer of the filtered solution, suitably diluted if necessary, at the maximum at 261 nm. At the same time measure the absorbance (1.6) at the maximum at 261 nm of a solution containing 0.1 mg of fluconazole RS per ml in the dissolution medium, using the same solution as the blank.

For each of the capsules tested, calculate the total amount of fluconazole \((\text{C}_{13}\text{H}_{12}\text{F}_{2}\text{N}_{6}\text{O})\) in the medium from the absorbances obtained and from the declared content of \(\text{C}_{13}\text{H}_{12}\text{F}_{2}\text{N}_{6}\text{O}\) in fluconazole RS. Use the requirements as described under 5.5 Dissolution test for solid oral dosage forms, Acceptance criteria to evaluate the results: The amount in solution is not less than 75% \((Q)\) of the amount declared on the label.

Assay

Either test A or B may be applied.

A. Mix the contents of 20 capsules and transfer a quantity containing about 50 mg of Fluconazole, accurately weighed, to a 10 ml volumetric flask, and dilute to volume with hydrochloric acid (~4 g/l) TS. Shake to dissolve, filter a portion of this solution and dilute 10 ml of the filtered solution to 25 ml with the same solution. Measure the absorbance of a 1 cm layer at the maximum at about 261 nm.

At the same time measure the absorbance of a solution of 0.2 mg of fluconazole RS per ml of hydrochloric acid (~4 g/l) TS, prepared and examined in the same manner, and calculate the percentage content of fluconazole \((\text{C}_{13}\text{H}_{12}\text{F}_{2}\text{N}_{6}\text{O})\) in the capsules, using the declared content of \(\text{C}_{13}\text{H}_{12}\text{F}_{2}\text{N}_{6}\text{O}\) in fluconazole RS.
B. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5μm). (Capcell Pak® C18 MGII (4.6x250 mm, 5μm) has been found suitable.) As the mobile phase, use a mixture of 86 volumes of a (0.63 g/l) solution of ammonium formate R and 14 volumes of acetonitrile R.

Prepare the following solutions in the mobile phase. For solution (1) use an amount of the mixed contents of 20 capsules to produce a solution containing 0.5 mg of Fluconazole per ml and filter the solution. For solution (2) use 0.5 mg of fluconazole RS per ml. For solution (3) use a solution containing 0.01 mg of fluconazole impurity C RS per ml and 1 mg of fluconazole RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 260 nm.

Inject separately 20 μl of each of solutions (1), (2) and (3). The test is not valid, unless in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity C and to fluconazole is at least 3.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the percentage content of fluconazole (C₁₃H₁₂F₂N₆O) in the capsules, using the declared content of C₁₃H₁₂F₂N₆O in fluconazole RS.

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**Fluconazoli injectio**

**Fluconazole injection**

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**Description.** A clear, colourless solution.

**Category.** Antifungal.

**Storage.** Fluconazole injection should be kept in a tightly closed container, protected from light.

**Additional information.** Strength in the current WHO Model List of Essential Medicines: 2 mg/ml in vial.

**Requirements**

Complies with the monograph for «Parenteral preparations».
**Definition.** Fluconazole injection is a sterile solution of Fluconazole in Water for injections.

The solution is sterilized by a suitable method (see 5.8 Methods of sterilization). Fluconazole injection contains not less than 90.0% and not more than 110.0% of the amount of fluconazole (C\textsubscript{13}H\textsubscript{12}F\textsubscript{2}N\textsubscript{6}O) stated on the label.

**Identity tests**

Either test A and C or test B and C may be applied.

A. 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 80 volumes of dichloromethane R, 20 volumes of methanol R, and 1 volume of ammonia (~260 g/l) TS solution as the mobile phase. Apply separately to the plate 20 μl of each of the following three solutions. For solution (A) use the injection to be examined. For solution (B) use 2 mg of fluconazole RS per ml in methanol R. For solution (C) use a mixture of 2 mg of fluconazole RS per ml and 2 mg of fluconazole impurity C RS per ml in methanol R. After application allow the spots to dry in a current of air. Develop the plate. After removing the plate from the chromatographic chamber, allow it to dry in a current of air, and 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). The test is not valid, unless the chromatogram obtained with solution (C) shows two clearly separated spots.

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given under Assay. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

C. Dilute a volume of the injection containing 2 mg of Fluconazole to 10 ml with water R. The absorption spectrum (1.6) of the resulting solution, when observed between 230 nm and 300 nm, exhibits maxima at 261 nm and 267 nm, and a minimum at about 264 nm. The ratio of the absorbance of a 1 cm layer at the maximum at about 261 nm to that at the minimum at about 264 is about 1.4.

**pH value (1.3).** pH of the injection, 4.0–6.0.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions given below under Assay. Prepare the following solutions in the mobile phase. For solution (1) use the injection to be examined. For solution (2) dilute 5 volumes of solution (1) to 100 volumes, then dilute 1 volume of this solution to 10 volumes. For solution (3) use 0.02 mg of fluconazole impurity C RS per ml. For solution (4) mix 1 volume of solution (3) with 1 volume of solution (1).

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 260 nm.
Inject separately 20 μl each of solutions (1), (2), (3) and (4). Record the chromatograms for about 3.5 times the retention time of fluconazole.

The peaks are eluted at the following relative retentions with reference to fluconazole (retention time about 11 minutes): impurity B about 0.4; impurity A about 0.5; impurity C about 0.8.

The test is not valid unless, in the chromatogram obtained with solution (4), the resolution between the peaks due to impurity C and to fluconazole is at least 3.0.

In the chromatogram obtained with solution (1),

- The area of any peak corresponding to impurity A is not greater than 0.8 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%),
- The area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.5 is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);
- The area of any peak corresponding to impurity C is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);
- The area of any other impurity peak, other than the principal peak, is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (3) (0.2%),
- The sum of the corrected area of any peak corresponding to impurity B and the areas of all peaks, other than the peak due to fluconazole, is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

**Assay**

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5μm). (Capcell Pak® C18 MGII (4.6x250 mm, 5μm) has been found suitable.)

As the mobile phase, use a mixture of 86 volumes of a (0.63 g/l) solution of ammonium formate R and 14 volumes of acetonitrile R.

Prepare the following solutions in the mobile phase. For solution (1) dilute 5.0 ml of the injection to be examined to 20.0 ml. For solution (2) use 0.5 mg of fluconazole RS per ml. For solution (3) use a solution containing 0.01 mg of fluconazole impurity C RS per ml and 1 mg of fluconazole RS per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 260 nm.

Inject separately 20 μl of each of solutions (1), (2) and (3). The test is not valid, unless in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity C and due to fluconazole is at least 3.0.
Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the percentage content of fluconazole (C₁₃H₁₂F₂N₆O) in the injection, using the declared content of C₁₃H₁₂F₂N₆O in fluconazole RS.

**Bacterial endotoxins.** Carry out the test as described under 3.4 Test for bacterial endotoxins.; contains not more than 0.416 IU of endotoxin RS per mg of Fluconazole.