

# WHO Drug Information

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

**Note:**

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

# Norms and standards

## Assessing new medical products in health emergencies: the EUAL procedures

Development and regulatory approval of medical products typically take many years. When an unprecedented Ebola outbreak devastated West African countries and kept on spreading, there were no approved vaccines, medicines or rapid diagnostic tests available to combat the disease. A WHO-convened ethical panel reached consensus that in this special situation, and provided certain conditions were met, it was ethical to use investigational products.

In the months that followed, WHO not only convened global players to accelerate R & D for Ebola, but also developed rules on how to identify those investigational products that can be used in an emergency – with the agreement of the competent regulatory authority – while they are being studied further. The Emergency Use Assessment and Listing (EUAL) procedures are the first of their kind of a global nature. They are a step ahead in ensuring that the world is prepared for future emergencies.

### Unmet medical needs

New medical products are approved every year to treat the diseases that continue to threaten the world's populations, such as cancer or diabetes. Research and development (R & D) and regulatory approval of new products typically take many years and require long-term planning of investments.

Ebola outbreaks have been known to occur since 1976 (1), but they were always quickly contained with infection control measures. When an Ebola outbreak was confirmed in March 2014, there was no approved medical product for the prevention or treatment of Ebola virus disease. However, this outbreak turned out to be unprecedented in size and complexity, with over 27 000 cases and 11 000 deaths on record in the most recent WHO Ebola Situation report (2). On 8 August 2014 the WHO Director-General

declared the Ebola outbreak to be a public health emergency of international concern.

Vaccines, treatments and diagnostics were now urgently needed to contain the outbreak, save lives and relieve suffering. On 11 August 2014 a WHO-convened panel reached consensus that in the particular circumstances of the Ebola outbreak, and provided certain conditions are met, it is ethical to offer unproven interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans as potential treatment or prevention (3).

### WHO leadership

The panel of independent experts who reviewed WHO's response to the Ebola outbreak has commended the Organization for stepping up to fill a void

*"We now know that the urgency of saving lives can accelerate R&D. We will harness this positive experience to develop a global R&D preparedness framework so that if another major disease outbreak ever happens again, for any disease, the world can act quickly and efficiently to develop and use medical tools and prevent a large-scale tragedy."*

Marie Paule Kieny,  
WHO Assistant Director-General  
and WHO Ebola R & D team lead

at a critical stage of the Ebola outbreak (4). WHO's Ebola R & D team successfully convened international partners to fast-track the development of needed products and provided leadership in the conduct of trials for candidate vaccines and in the use of experimental therapies such as drugs and blood products.

When this race for time began, there was no guidance available on how to test any candidate products in an emergency situation, or how to regulate them. The Regulation group of the WHO Ebola R & D team rose to the task and worked against the clock to propose a new model for rapid assessment of investigational vaccines, medicines and diagnostics to be used in emergencies. The Emergency Use Assessment and Listing (EUAL) procedures were published for comment on 10 March 2015. A consultation period of four weeks followed, leading to useful input being received from regulators, industry and other stakeholders. The final EUAL procedures were published on 10 July 2015 (5).

### The EUAL procedures

The EUAL procedures are reproduced in [Attachment 1](#). They define a voluntary pathway for manufacturers to have their as yet unregistered products listed as acceptable for use in a public health emergency, based on a minimum set of available quality, safety, and efficacy data. It is then up to the regulatory authorities of

target countries to authorize the use of the listed products in their territories.

WHO regulatory experts have long-standing experience in identifying the best options of providing needed treatment when stringently approved products are out of reach. The WHO Prequalification Team (PQT) assesses vaccines, medicines and diagnostic products for use in UN and donor-funded programmes. The head of the Ebola R&D Regulation group and most of its members came from PQT, and the group could thus draw on a vast amount of experience with regulation and manufacturing of medical products. The EUAL procedures are the outcome of team work across all three product categories that were needed to address the Ebola crisis.

In this context it is important to note that there are fundamental differences between WHO prequalification and the EUAL procedure. Prequalification focuses mainly on the ongoing quality of products whose safety and efficacy – or performance for diagnostics – have been demonstrated upfront. EUAL, on the other hand, is based on assessment of available data for yet unproven candidate products that are to be used in an emergency while additional safety and efficacy data are being generated.

So far, four Ebola diagnostic tests have been listed under this procedure (6), and WHO has published an interim guidance document for Ministries of Health and

other organizations on factors to consider in the selection and use of available in vitro diagnostic (IVD) assays for Ebola virus disease (7). As the world is on the verge of an effective Ebola vaccine (see page 345), the VSV-EBOV vaccine could also become a candidate for EUAL.

### Preparedness for future emergencies

Lessons have been learned from the Ebola outbreak. The Ebola Interim Assessment Panel has noted that research and development for neglected diseases remains inadequate, and has recommended that WHO should play a central convening role in research and development efforts in future emergencies.

New health emergencies will certainly arise. Three new pathogens have emerged since the year 2000 – SARS, H7N9 avian influenza and the MERS coronavirus – and in May 2015 the WHO Director General warned that the threat from avian influenza is persisting to the point where the world should be on high alert (8).

Reforms and assured core funding will be required for WHO to fully play its normative role in a complex and changing health architecture. Whatever the framework will be to manage future public health emergencies, the EUAL procedures will be a valuable tool to guide manufacturers and regulatory professionals in bringing new medical products promptly to affected populations.

### Acknowledgements

WHO wishes to thank all those who contributed to the development of the EUAL procedures, including the US Food and Drug Administration (USFDA), the

European Medicines Agency (EMA), GlaxoSmithKline (GSK), Janssen-Cilag, the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and others as well as WHO's own staff and consultants. Without their dedicated work and constructive input, the EUAL procedures could not have been put forward at a time when they were urgently needed.

### References

- 1 WHO. Ebola Situation Report – 5 August 2015 [web page]. <http://apps.who.int/ebola/current-situation/ebola-situation-report-5-august-2015>.
- 2 WHO. Ebola virus disease. Fact sheet N°103. Updated April 2015.
- 3 Ethical considerations for use of unregistered interventions for Ebola virus disease (EVD). Summary of the panel discussion. WHO Statement, 12 August 2014.
- 4 Report of the Ebola Interim Assessment Panel. 15 July 2015.
- 5 WHO Emergency use assessment and listing procedures for medical products during public health emergencies. Published 10 July 2015, available at: [www.who.int/medicines/news/public\\_consult\\_med\\_prods/en/](http://www.who.int/medicines/news/public_consult_med_prods/en/).
- 6 WHO In vitro diagnostics and laboratory technology. Emergency Use Assessment and Listing (EUAL) Procedure for Ebola Virus Disease (IVDs) [web page]. [www.who.int/diagnostics\\_laboratory/procurement/purchasing/en/](http://www.who.int/diagnostics_laboratory/procurement/purchasing/en/).
- 7 WHO. Emergency guidance. Selection and use of Ebola in vitro diagnostic (IVD) assays. June 2015. WHO/EVD/HIS/EMP/15.2. Geneva, Switzerland: WHO, 2015.
- 8 WHO Director-General's speech at the Sixty-eighth World Health Assembly. 18 May 2015.

# Attachment 1: Emergency Use Assessment and Listing Procedures (EUAL) for candidate vaccines, medicines and diagnostics

## Introduction

The 2014-15 Ebola outbreak is the largest Ebola epidemic in history, which affected multiple countries in West Africa. This epidemic has demonstrated the need for a WHO emergency use assessment and listing procedure (EUAL) for candidate [vaccines / medicines / in vitro diagnostics (IVDs)] for use in the context of a public health emergency. The purpose of this extraordinary procedure is to provide guidance to interested UN procurement agencies and national regulatory authorities (NRAs) of relevant member states. The present document describes the EUAL for candidate [vaccines / medicines / IVDs] and is primarily aimed at manufacturers of these medicines in the context of use during a public health emergency. Participation in the procedure is voluntary.

### EUAL is not WHO prequalification, and should not be thought of as such.

Rather, EUAL is a special procedure for medicines in the case of a public health emergency when the community may be willing to tolerate less certainty about the efficacy and safety of products, given the morbidity and/or mortality of the disease and the shortfall of treatment and/or prevention options. In such instances, it is paramount to determine the minimal level of information needed prior to making a product available under a time-limited EUAL, while further data are being gathered and evaluated.

WHO recognizes the prime importance of conducting and completing clinical trials of any novel product, including when used in a public health emergency. The inclusion of a product in the EUAL list should not compromise such trials.

WHO has developed the EUAL procedure to expedite the availability of [vaccines / medicines / IVDs] needed in public health emergency situations. The EUAL procedure is intended to assist interested UN procurement agencies and Member States on the acceptability for use of a specific [vaccine / medicine / IVD] in the context of a public health emergency, based on a minimum set of available quality, safety, and efficacy data.

It should be noted that it is the sole prerogative of WHO Member States whether or not to allow the emergency use of a candidate [vaccines / medicines / IVDs] in their country.

Vaccines	Medicines	Diagnostics
<p><b>Eligibility</b></p> <p>In order to qualify for an EUAL, the use of the vaccine must meet the following conditions:</p> <ul style="list-style-type: none"> <li>• The disease for which the vaccine is intended has been declared by the WHO Director-General to be a Public Health Emergency of International Concern (PHEIC). The Director-General may authorize use of this procedure for a public health emergency that does not meet the criteria of a PHEIC if s/he determines that this is in the best interest of public health.</li> <li>• Based on the contingencies of the specific public health emergency, it is reasonable to consider the vaccine for EUAL assessment (e.g., there is no licensed vaccine for the indication or for a critical subpopulation, e.g. children, or there is a specific vaccine shortage).</li> </ul>	<p><b>Eligibility</b></p> <p>In order to qualify for an EUAL, the use of the medicine must meet the following conditions:</p> <ul style="list-style-type: none"> <li>• The disease for which the medicine is intended has been declared by the WHO Director-General to be a Public Health Emergency of International Concern (PHEIC). In a public health emergency that does not rise to the level of a PHEIC, the Director-General may authorize use of this procedure if s/he determines that this is in the best interest of public health.</li> <li>• Based on the contingencies of the specific public health emergency, it is reasonable to consider a medicine for EUAL assessment e.g., there are no licensed medicines for the indication or for a critical subpopulation</li> </ul>	<p><b>Eligibility</b></p> <p>In order to qualify for an EUAL, the use of the IVD must meet the following conditions:</p> <ul style="list-style-type: none"> <li>• The disease for which the IVD is intended has been declared by the WHO Director-General to be a Public Health Emergency of International Concern (PHEIC). In a public health emergency that does not rise to the level of a PHEIC, the Director-General may authorize use of this procedure if s/he determines that this is in the best interest of public health.</li> <li>• Based on the contingencies of the specific public health emergency, it is reasonable to consider the IVD for EUAL assessment e.g., there are no IVDs that have undergone comprehensive premarket regulatory assessment for the indication or for a critical subpopulation (e.g., children), or there is a specific IVD shortage.</li> </ul>



***EUAL – Vaccines  
(continued)***

- The vaccine is subject to oversight by a NRA that has been assessed as functional by WHO and is willing to provide oversight of batch release and other post-EUAL product safety and manufacturing quality assurance requirements.
- The vaccine is manufactured in compliance with current Good Manufacturing Practices (GMP). If a manufacturer has a documented acceptable history of quality manufacturing of vaccines, WHO may waive the requirement for conducting an on-site inspection.
- The vaccine applicant attests that it intends to complete the development of the product and apply for WHO prequalification. In the ideal situation, the remaining clinical trials and other requisite testing will already be underway at the time of the application for an EUAL. (N.B. A future prequalification application should incorporate all information submitted for the EUAL plus any other information needed to complete a prequalification application.)

WHO may consider reviewing a candidate vaccine for EUAL that does not meet all of the above requirements. In such situations, the application letter and documentation provided to WHO must substantiate the need for the product although it does not meet all eligibility requirements.

WHO will conduct a screening of the application and documentation, and will inform the applicant within 5 working days whether the application can be accepted for evaluation. The approximate review time frame will be communicated after the screening process.

By submitting an application the manufacturer will be deemed to have accepted the terms of this procedure.

**Content of the application**

The EUAL process will assess whether, in light of available WHO/international standards, the submitted data demonstrate

***EUAL – Medicines  
(continued)***

- (e.g., children), or there is a specific medicine shortage.
- The medicine (both API and FFP) is manufactured in compliance with current Good Manufacturing Practices (GMP). If a manufacturer has a documented acceptable history of quality manufacturing of medicines, WHO may waive the requirement for conducting an on-site inspection.
- The applicant attests that it intends to complete the development of the product and apply for WHO prequalification. In the ideal situation, the remaining clinical trials and other requisite testing will already be underway at the time of the application for an EUAL. (N.B. A future prequalification application should incorporate all information submitted in the EUAL plus any other information needed to complete a prequalification application.)

WHO may consider reviewing a candidate medicine for EUAL that does not meet all of the above requirements. In such situations, the application letter and documentation provided to WHO must substantiate the need for the product although it does not meet all eligibility requirements. WHO will conduct a screening of the application and documentation, and will promptly inform the applicant whether the application can be accepted for evaluation. The approximate review time frame will be communicated after the screening process.

By submitting an application the manufacturer will be deemed to have accepted the terms of this procedure.

***EUAL – Diagnostics  
(continued)***

- The applicant must be the legal manufacturer of the product. A condition for the EUAL of a “re-branded”<sup>1</sup> product is that the original product manufacturer and the “re-brander” explicitly consent to the public disclosure by WHO of this “re-branding” arrangement.
- The IVD is manufactured under a functional quality management system (QMS) and the manufacturer has the capacity to meet expected demand.
- The IVD manufacturer attests that it intends to complete the validation and verification of the product and apply for WHO prequalification. In the ideal situation, the remaining prequalification requisite testing will already be underway at the time of the application for an EUAL (N.B. A future prequalification application should incorporate all information submitted in the EUAL plus any other information needed to complete a prequalification application).

WHO may issue an Expression of Interest (EOI) regarding IVDs that might be eligible for an EUAL assessment. Such an EOI may be either open-ended or for a fixed period of time. The EOI will identify those IVDs that are to be prioritized in the EUAL process. This prioritization procedure will take into account any target product profiles (TPP) established by WHO for IVDs in response to the public health emergency. If the application is not for a priority product but for a product that may still be of interest during the public health emergency, WHO may choose to assess the product, but those fitting the priority criteria (for example, one fulfilling a WHO TPP) will be assessed first.

WHO may consider reviewing a candidate IVD for EUAL that does not meet all of the above requirements.

<sup>1</sup> A product that is manufactured under identical conditions at the same manufacturing site(s) as the original product. In other words, a “rebranded” product is identical in every aspect to the product manufactured by the original manufacturer, except that the product is labeled with the “rebranded” product name and purchaser identifier.

**EUAL – Vaccines**  
(continued)

a reasonable likelihood that the vaccine quality, safety and effectiveness are acceptable, and that the benefits outweigh the foreseeable risks and uncertainties in the context of a PHEIC.

The application must be submitted to WHO and must provide the following information:

- Production and quality control information: starting materials (characterization of cell banks, organism seeds, and recombinant constructs), production process, quality control of intermediate and finished products, testing methods, including validation, specifications, and justification, proposed parameters, and values for batch release.
- Evidence of GMP compliance for the manufacturing site(s) where the vaccine is being produced.
- Stability data to demonstrate that the vaccine will maintain the minimum potency considered to be immunogenic/efficacious for the claimed shelf life under the conditions of use.
- Summary information on preclinical and clinical data (safety, immunogenicity, and efficacy, if available). If considered necessary, WHO may require the submission of raw data. If it is not possible to obtain human efficacy data, the applicant will have to justify to WHO's satisfaction that immunogenicity data are sufficient under the circumstances. This should include correlates of protection, if available. In those cases where human efficacy data and/or correlates of protection are not available at the time of EUAL submission, and WHO decides to include the product in the EUAL list, WHO will require the manufacturer to submit such data and correlates to WHO as soon as they are available.
- Proposed labelling.
- A plan to monitor quality, safety and efficacy in the field, and an undertaking to submit any new data to WHO as soon as the new data are available.

**EUAL – Medicines**  
(continued)

**Content of the application**

The EUAL procedure will assess whether, in light of available WHO/international standards, the submitted data demonstrate a reasonable likelihood that the medicine quality, safety and effectiveness are acceptable, and that the benefits outweigh the foreseeable risks and uncertainties in the context of a PHEIC.

The application must be submitted to WHO and must provide the following information:

- Certificate(s) or other acceptable evidence of GMP compliance for the relevant manufacturing site(s) used in the production of the product,
- Stability data to demonstrate that the medicine will maintain the minimum potency considered necessary for the claimed shelf-life under the conditions of use,
- Sufficient chemistry, manufacturing, and controls data to assure the quality of the product for its intended purpose,
- Summary information on all preclinical and clinical data. If it has not been possible to obtain efficacy data in humans, the applicant should provide all other available data substantiating to WHO's satisfaction, the claim of the medicine's efficacy and safety under the conditions of the foreseen use. This should include any surrogates (validated or otherwise) that are thought to be predictive of ultimate clinical benefit. In these cases, where human efficacy data are not available at the time of EUAL submission, and WHO decides to include

**EUAL – Diagnostics**  
(continued)

In such situations, the application letter and documentation provided to WHO must substantiate the need for the product although it does not meet all eligibility requirements. WHO will conduct a screening of the application and documentation and will inform the applicant within 5 working days whether the application can be accepted for evaluation. The approximate review time frame will be communicated after the screening process.

By submitting an application the manufacturer will be deemed to have accepted the terms of this procedure.

**Content of the application and minimum data requirements for emergency use listing:**

The EUAL procedure will assess, against current WHO/international standards, where available if the submitted evidence is sufficient to demonstrate that the benefits of using the IVD outweigh the foreseeable risks and uncertainties in the context of a PHEIC. As such, the EUAL process will consist of:

- A desktop review of selected manufacturing and QMS documentation;
- A review of any existing documentary evidence of safety and performance; and
- A limited laboratory evaluation of relevant performance and operational characteristics of the product.

Specific data requirements may require clarification and discussion between the applicant and WHO. Applicants are highly encouraged to contact WHO as early as possible to discuss specifics of their application.

The application must be submitted to the WHO and must provide the following information, if available:

**Labelling:**

- Labels (all components, kit, instrument(s) and/or box labels);
- Instructions for use (IFU) and user manual of instrument(s) (if applicable); and



***EUAL – Vaccines  
(continued)***

- A plan to help assure that prospective recipients and healthcare providers are adequately informed about the uncertainties regarding both the potential benefits and risks.

**Minimum data requirements for emergency use listing:**

Specific data requirements may require clarification and discussion between the applicant and WHO. Applicants are highly encouraged to contact WHO as early as possible to discuss specifics of their application.

**Manufacturing Quality Data:**

- (1) Full characterization of cell banks according to WHO TRS 978, and any subsequent updates.
- (2) Full characterization of master and working seed organism(s), based on reference to the most appropriate WHO TRS. Process validation and demonstration of consistency of production at the production scale used for the lots to be distributed. If WHO deems it appropriate, interim process validation data based on pilot scale batches can be reviewed. N.B., if full characterisation is not possible at the time of submission, adequate justification must be submitted as to why this is not possible, and a plan must be presented to adequately address the data gaps.
- (3) Justified specifications for starting material, intermediates, and final products.
- (4) Validation of potency test (or initial interim data as available).
- (5) Stability data for the vaccine at the production scale of the vaccine to be deployed. For vaccines being assessed for emergency use, WHO and if convened, the WHO Ad Hoc Committee for the Emergency Use of Vaccines (AACEUV – see below), will consider suitability of the vaccine in national immunization programme of developing countries (programmatic

***EUAL – Medicines  
(continued)***

- the product in the EUAL list, WHO will require the manufacturer to submit such data to WHO as soon as they are available
- Proposed labelling
- A plan to monitor quality, safety and efficacy in the field, and an undertaking to submit any new data to WHO as soon as the new data are available,
- A plan to help assure that prospective patients and healthcare providers are adequately informed about the uncertainties regarding both the potential benefits and risks.

**Minimum data requirements for emergency use listing:**

Specific data requirements may require clarification and discussion between the applicant and WHO. Applicants are highly encouraged to contact WHO as early as possible to discuss specifics of their application.

**Manufacturing Quality Data:**

- (1) Information on the active ingredient(s) and finished product, including characterization, composition, preparation, controls (specifications), known and potential impurities. A list of intended changes for scale up, if any, along with a discussion on impact of these changes on the safety/efficacy profile of the product should also be provided.
- (2) Stability data for the finished product at a scale commensurate with safe use under the conditions of a public health emergency. For medicines being assessed for emergency use, WHO and the WHO Ad Hoc Committee for the Emergency Use of

***EUAL – Diagnostics  
(continued)***

- Any other instructional materials provided to the user.
- Proposed labelling
- A plan to help assure that prospective recipients and healthcare providers are adequately informed about the uncertainties regarding both the potential benefits and risks.

**Product Performance Specification, and Associated Validation and Verification Studies**

Studies in support of the intended use are requested. Where they exist, these would include:

- Specimen type
  - Accuracy of measurement: trueness and precision studies.
  - Analytical sensitivity
  - Analytical specificity: interference and cross reactivity studies
  - Traceability of calibrators and control material values
  - Measuring range of the assay
  - Validation of assay cut-off
  - Validation of assay procedure – reading time
  - Stability (excluding specimen stability)
  - Claimed shelf life
  - In-use stability
  - Shipping stability
  - Robustness Studies
  - Evaluation of potential biohazard issues associated with the design and use of the product
  - Clinical evidence (evidence of relevant performance characteristics such as clinical or diagnostic sensitivity and specificity) depending on the feasibility of conducting such studies given the emergency circumstances
- This list may be subject to change to meet the needs of a particular disease state of IVD TPP.
- For each study to be submitted, the following must be provided:
- Study description, study identifier, product identifier (e.g., lot numbers), IFU version used, the date of initiation and the date of completion;
  - A summary of the study findings including a conclusion that clarifies how the study objectives have been met; and

### *EUAL – Vaccines (continued)*

suitability<sup>1</sup>) and may consider candidate vaccines with characteristics that would not be accepted for prequalification.

a. Vaccines requiring storage at less than -20°C are generally not accepted for prequalification. However, under this emergency provision, such vaccines can be considered. Upon receipt of such an application, WHO will evaluate and consider the feasibility of assistance to recipient countries with regard to infrastructure for vaccine storage and distribution at required temperatures.

b. Routinely, if the vaccine presented for prequalification requires storage below +2°C during its shelf-life period, it should have a minimum period of storage between +2°C and +8°C of 6 months. Under this emergency provision, vaccines with a shelf life at +2 to +8°C of less than 6 months can be considered. The application should include stability data at +2 to +8°C to determine the minimum acceptable storage period at +2 to +8°C. Upon receipt of such an application, WHO will evaluate and consider the feasibility of providing assistance to recipient countries with regard to infrastructure for vaccine storage and distribution at required temperatures.

c. Routinely, multi-dose vaccines for prequalification should contain adequate preservative, unless they are live-attenuated vaccines (where the preservative may have an adverse effect on the viability of the microbe). However, if a multi-dose vaccine submitted under this emergency provision does not contain a preservative, adequate information/plans on how such a vaccine could be safely managed in the field should be submitted.

### *EUAL – Medicines (continued)*

Medicines (ACEUM – see below), if convened, will consider suitability of the medicine in light of WHO treatment guidelines and may consider candidate medicines with characteristics that would not be accepted for prequalification.) and

(3) Inspection report(s) from an NRA or from a prequalification inspection (or paper assessment) showing compliance with the GMP requirements. (Based on the acceptability of the NRA report, WHO may or may not need to perform its own assessment of GMP compliance.)

#### **Non-clinical and Clinical Data:**

- (1) All relevant *in vitro* and *in vivo* pharmacodynamic data, e.g., on microbiologic activity (including any modeling performed).
- (2) Data demonstrating efficacy in animal model(s) under well-controlled and documented conditions. The preferred model for prediction of efficacy in humans depends on the disease and may vary according to the medicine's mechanism of action. The applicant must justify the choice of animal model.
  - a. Evidence of efficacy should include improved survival and/or reduced morbidity of animals in the preferred model under relevant conditions. Surrogate markers, validated or reasonably expected to predict efficacy, would be supportive.
  - b. All available evidence of the medicine's activity *in vitro* and in other animals, together with

### *EUAL – Diagnostics (continued)*

- The study protocol and full report.
- Quality management systems requirements
- Evidence of implementation of a manufacturing quality management system (e.g., ISO 13485:2003 certificate and most recent regulatory (or certification body) audit report, quality manual, exclusions or non-applications, list of valid quality management documentation, management review report);
- Details of the production workflow including QC points (in process and final release activities);
- Critical supplier list including supplied products (components/raw materials) and services;
- Details on the experience with the product (when was the product developed and when was it first placed on the market, if applicable);
- Details on the manufacturing capacity (existing inventory, minimum time to provide finished product, maximum batch/lot size).

#### **The assessment process – a triaged activity**

The assessment process itself is generally a sequential process with applications that do not pass a step not being eligible to continue in the process; however, the process will be flexible depending on the individual situation. This however, does not preclude preparatory planning for subsequent steps. At each step, the assessment considers the potential benefits weighed against known or predictable risks.

#### **STEP 1 – QMS Review**

A review of the manufacturer's QMS documentation and specific manufacturing documents is the first step in the process. At the conclusion of this step, the recommendation will be to proceed, request further documentation, or to terminate the application. The decision to proceed with the assessment process will be made if there is sufficient evidence that the applicant is the legal manufacturer, that there is evidence of an adequate QMS in place, and

<sup>1</sup> WHO/IVB/14.10

**EUAL – Vaccines**  
(continued)

(6) Inspection report(s) from the responsible NRA or from the WHO prequalification team showing compliance with the GMP requirements.

**Non-clinical and Clinical Data:**

- (1) Non-clinical data demonstrating acceptable safety, immunogenicity, and efficacy in the most appropriate animal model. The applicant must justify the choice of animal model. If the non-clinical package is not complete at the time of submission, the applicant must submit adequate justification for the lack of complete data and an adequate plan and timeline for submitting those data.
- (2) Clinical data demonstrating the appropriate dose to be used and initial acceptable safety and immunogenicity in the population in which the vaccine will be used in the context of the public health emergency.
- (3) Preliminary data showing some efficacy— if available. If preliminary human data showing some efficacy are not available for the vaccine under consideration and if not imminently available for other vaccines being concurrently developed, WHO will consider whether the preponderance of evidence from the non-clinical, and early human studies justifies considering the immunogenicity data as a potential surrogate that is thought to be reasonably predictive of clinical efficacy. In such cases, the emergency use listing can proceed, provided there are trials underway that will ultimately provide validation data for the surrogate. Safety and immunogenicity data from other vaccines made by the manufacturer using the same product platform may be considered as supportive data for review.

**Abbreviated EUAL Assessment**  
WHO may in part rely on a previous assessment through another

**EUAL – Medicines**  
(continued)

- pharmacokinetics and efficacy in humans against other diseases will be evaluated. Data provided should give reasonable assurance that an ineffective regimen will be excluded.
- (3) A rationale should be provided for the proposed dosing in humans, with reference to drug exposures shown to be effective in suitable models. Ideally, human pharmacokinetic data should be available, demonstrating similar levels of the drug following administration at the proposed dose, compared to blood levels found to be efficacious in the relevant animal model.
  - (4) A safety assessment should be provided for the drug at the exposure level proposed for treatment of the disease, considering non-clinical and, if available, clinical data. If human PK trials or studies in other indications at the exposure level proposed for treatment of the disease have been conducted, assessment of safety using standard parameters (e.g., adverse events, clinical laboratory monitoring, etc.) will serve as the most meaningful assessment of safety, supplemented by any other non-clinical and clinical data at different exposure levels. Safety results from animal studies, as well as relevant in vitro data should be assessed with respect to safety in humans. and
  - (5) Clinical data demonstrating safety and efficacy at the dose to be used and initial acceptable efficacy and safety in the population where the medicine will be used in the context of the

**EUAL – Diagnostics**  
(continued)

that the requisite manufacturing capability exists.

**STEP 2 – Dossier Review**

The second step is the assessment of the documentary evidence of safety and performance. It is acknowledged that many of the required studies to meet full regulatory requirements may not have been performed for IVDs undergoing EUAL assessment. Based on the submitted documentation, a risk based judgment will be made on whether there is a favorable benefit/ risk profile. An initial evidence base that includes studies using banked specimens from previous studies, relevant studies in the literature, and studies using contrived specimens to supplement testing of clinical specimens including representative analytes may be acceptable in the absence of complete analytical and/ or clinical performance studies, if this evidence base provides a reasonable assurance of safety and performance.

In some jurisdictions, minimizing potential harm of an IVD approved through an emergency authorization mechanism is achieved by active post-market surveillance. However, it cannot be always be assumed that, in the public health emergency settings this EUAL process serves, that there are sufficient resources and institutions in place for any consistent effective surveillance. It will be critical for the manufacturer to detail what, if any, post-emergency-use-listing safety monitoring activities are planned if the EUAL is granted.

The outcome of this step will determine if the application will proceed to step 3, whether further documentation should be requested, or whether the application should be terminated.

**STEP 3 – Performance Evaluation**

When needed and where possible, WHO will work with relevant partners and WHO Collaborating Centres to undertake a limited performance evaluation to verify critical analytical and clinical performance characteristics of the product and to make preliminary assessments

**EUAL – Vaccines**  
(continued)

emergency mechanism performed by a functional NRA.

However, as WHO EUAL is designed to provide assurance of the quality, safety, and efficacy of vaccines for use in a current public health emergency, WHO may still undertake some extra assessment activities if deemed necessary.

**Different assessment procedures based on specific circumstances**

Based on specific circumstances related to the level of regulatory oversight of the manufacturing of the product and the experience of the manufacturer with regard to prequalification, the contents of the application and the assessment procedure may vary as follows:

**Category A**

*Criteria:*

- Responsible<sup>2</sup> NRA has a collaboration agreement with the WHO prequalification programme for streamlining<sup>3</sup> (or the formalization of an agreement is in process)
- Full reports from the responsible NRA with basis for the decision to authorize emergency use are available

*WHO assessment approach:*

- WHO, and if convened, the AACEUV will conduct an accelerated review of:
  - Report(s) from the responsible NRA (Summary basis for the emergency use approval or equivalent)
  - Programmatic aspects<sup>4</sup>

**Category B**

*Criteria:*

- Manufacturer has other prequalified products and successfully sustained prequalification status for 5 years or more

*WHO assessment approach:*

<sup>2</sup> An NRA that has been assessed by WHO as functional for vaccine regulatory oversight

<sup>3</sup> See WHO TRS 978 – Annex 6

<sup>4</sup> WHO/IVB/14.10

**EUAL – Medicines**  
(continued)

public health emergency. If large scale study results are not available, WHO will consider whether the preponderance of evidence from the pre-clinical and early human studies, and any other information of which it is aware, justifies reliance on an unvalidated surrogate thought to be reasonably likely to predict clinical efficacy. In such cases the emergency use listing can proceed provided there are trials underway which it is expected will provide clinical validation of the surrogate.

**Abbreviated EUAL Assessment**

WHO may in part rely on a previous assessment through another emergency mechanism, if the review of the other emergency mechanism is deemed to be of a satisfactory standard.

However, WHO EUAL is designed to provide a level of assurance of the quality, safety, and efficacy of these medicines for the primary purpose of use in the setting of a current public health emergency. This focus means that WHO may still undertake some extra assessment activities if deemed necessary.

**Ad hoc Advisory Committee for the Emergency Use of Medicines (AACEUM)**

As part of the evaluation of an EUAL application, WHO may (but does not have to)<sup>1</sup> convene a meeting of the ad hoc advisory committee for the emergency use of medicines (AACEUM) to assess the information in the product EUAL application and other information available to the

<sup>1</sup> See Terms of Reference of the AACEUM

**EUAL – Diagnostics**  
(continued)

regarding its utility in different settings. Protocols will be drafted and comment sought from the participating WHO laboratories or WHO Collaborating Centres, and where time permits, more widely. Ethics approval both from WHO and in country will be sought, as appropriate. Special attention will be paid to the suitability of use for the intended setting.

Acceptance criteria will be established for the critical performance characteristics, but will take into account the limitations of the scale of the evaluation, and the potential clinical utility of the IVD in the context of the PHEIC.

If the acceptance criteria have been met, the application will be deemed to have successfully met WHO laboratory performance requirements for EUAL.

**Abbreviated EUAL Assessment**

Some submissions submitted for WHO EUAL may have undergone a previous assessment through other emergency mechanisms, for example, the US FDA Emergency Use Authorization (EUA) process. Where this is the case, it is not the intent of WHO to undertake duplicative work, if the review of the other emergency mechanism is deemed to be of a satisfactory standard. The ability to waive aspects of the EUAL assessment in these circumstances can be applied to any of the three steps. In situations where independently generated performance data are available, WHO may also consider using these data in place of or to reduce the extent of a WHO-coordinated performance evaluation.

However, WHO EUAL is designed to provide a level of assurance of the quality, safety, and performance of these assays for the primary purpose of use in the setting of a current public health emergency. This focus means that WHO may still undertake some extra assessment activities if deemed necessary.



**EUAL – Vaccines**  
(continued)

WHO, and if convened, AACEUV will conduct an accelerated review of:

- Application (see above for required content)
- Programmatic aspects<sup>5</sup>

**Category C****Criteria:**

- Manufacturer does not have other prequalified products or some of its products have been delisted in the preceding 5 years.

**WHO assessment approach:**

WHO, and if convened, AACEUV will conduct a review of:

- Application (see above for required content)
- Inspection report from PQ
- Programmatic aspects<sup>5</sup>

**Ad hoc Advisory Committee for the Emergency Use of Vaccines (AACEUV)**

As part of the evaluation of an EUAL application, WHO may (but does not have to<sup>6</sup> convene a meeting of the ad hoc advisory committee for the emergency use of vaccines (AACEUV) to assess the information in the product EUAL application and other information available to the committee.

Upon completion of its review, the committee will issue an opinion and provide advice to WHO on the acceptability of the vaccine for emergency use in the context of the public health emergency.

This opinion will be advisory to WHO. The final decision whether or not to include a product in the EUAL list will rest with WHO.

The Committee will be selected by the Essential Medicines and Health Products Department of WHO primarily from suitably qualified members of other standing advisory committees, relevant WHO expert panels, and other suitably qualified experts, including representatives from the NRA in the country of manufacture and NRA(s) from the country/-ies in which the product

<sup>5</sup> WHO/IVB/14.10

<sup>6</sup> The criteria are included in the Terms of Reference of the AACEUV

**EUAL – Medicines**  
(continued)

committee. Upon completion of its review, the committee will issue an opinion on the acceptability of the medicine for emergency use in the context of the public health emergency. This opinion will be advisory to WHO. The final decision whether or not to include a product in the EUAL list will rest with WHO.

The Committee will be selected by the Essential Medicines and Health Products Department of WHO primarily from suitably qualified members of other standing advisory committees, relevant WHO expert panels, and other suitably qualified experts, including representatives from the NRA in the country of manufacture and NRA(s) from the country/-ies in which the product would be used. If possible, the committee should include at least two representatives from the geographical area(s) of the public health emergency. All members of the AACEUM will be required to complete the WHO Declaration of Interest form for WHO experts.

If the committee cannot develop an opinion by consensus, any dissenting views must be noted in the report.

**WHO Decision on Emergency Use Listing**

Upon making a decision (in its sole discretion) to include a candidate medicine in the list of products deemed to have an acceptable quality, safety and effectiveness, which outweigh the foreseeable risks, in the context of use in a public health emergency of international concern, WHO will - subject to protection of confidential information of the applicant - publish a report of

**EUAL – Diagnostics**  
(continued)**Ad hoc Advisory Committee for the Emergency use of IVDs (AACEUD)**

As part of the evaluation of an EUAL application, WHO may (but does not have to<sup>2</sup> convene a meeting of the ad hoc advisory committee for the emergency use of IVDs (AACEUD) to assess the information in the product EUAL application and other information available to the committee. Upon completion of its review, the committee will issue an opinion on the acceptability of the IVD for emergency use in the context of the public health emergency. This opinion will be advisory to WHO. The final decision whether or not to include a product in the EUAL list will rest with WHO.

The Committee will be selected by the Essential Medicines and Health Products Department primarily from suitably qualified members of other standing advisory committees, relevant WHO expert panels, and other suitably qualified experts, including representatives from the NRA in the country of manufacture and NRA(s) from the country/-ies in which the product would be used. If possible, the committee should include at least two representatives from the geographical area(s) of the public health emergency. All members of the AACEUD will be required to complete the WHO Declaration of Interest form for WHO experts.

If the committee cannot develop an opinion by consensus, any dissenting views must be noted in the report.

**WHO Decision on Emergency Use Listing**

Upon making a decision (in its sole discretion) to include a candidate IVD in the EUAL list of products deemed to have benefits that outweigh the foreseeable risks and uncertainties for use in a public health emergency of international concern, WHO will - subject to the protection of confidential information of the applicant - publish a report of its assessment on the WHO website.

<sup>2</sup> The criteria are included in the Terms of Reference of the AACEUD

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(continued)

would be used). If possible, the committee should have at least two representatives from the geographical area(s) of the public health emergency. All members of the AACEUV will be required to complete the WHO Declaration of Interest form for WHO experts.

If the committee cannot develop an opinion by consensus, any dissenting views must be noted in the report.

**WHO Decision on Emergency Use Listing**

WHO may, prior to including a product in the list, consult and/or coordinate with relevant NRA(s) and other parties, as appropriate.

The decision made by WHO (in its sole discretion) to include a vaccine in the list is based on:

- information and documentation submitted which provide sufficient evidence (at the time of the assessment) regarding quality, safety, and efficacy/effectiveness and,
- a risk/benefit analysis, for use in a PHEIC.

WHO will subject to the protection of confidential information of the applicant publish a report of its assessment on the WHO website.

The EUAL list will be accompanied by general notes and disclaimers as outlined in Annex 1. In this connection, it should be noted that inclusion in the EUAL list does not constitute an endorsement, or warranty of the fitness, by WHO of any product for a particular purpose, including in regard to its safety and/or efficacy. The relevant authorities of WHO Member States shall be and remain exclusively responsible for authorizing the use of listed vaccines during a public health emergency in their country.

The validity of an emergency use listing in the context of a public health emergency will generally be for 12 months. All decisions for an emergency use listing will be reassessed within 12 months (or sooner, if further data or other information become available that

**EUAL – Medicines**  
(continued)

its assessment on the WHO website.

The EUAL list will be accompanied by general notes and disclaimers as outlined in Annex 1. In this connection, it should be noted that inclusion in the EUAL list does not constitute an endorsement, or warranty of the fitness, by WHO of any product for a particular purpose, including in regard to its safety and/or efficacy. The relevant authorities of WHO Member States shall be and remain exclusively responsible for authorizing the use of listed medicines during a public health emergency in their country.

WHO may, prior to including a product in the list, consult and/or coordinate with relevant NRAs and other parties as appropriate. The validity of an emergency use listing in the context of a public health emergency will generally be for 12 months. All decisions to grant an emergency use listing will be reassessed within 12 months (or sooner, if further data or other information become available that could alter the original opinion). When deemed necessary and warranted based on available data or information, the emergency use listing can be extended. Products may be taken off the EUAL list if new data or information become available that change the benefit-risk profile of the product, or immediately upon declaration by the WHO Director-General that there no longer is a PHEIC. Applicants are required to supply any new information/data to WHO as soon as it is available.

As WHO is responsible for the EUAL assessment, the ownership of the above mentioned reports lies

**EUAL – Diagnostics**  
(continued)

The EUAL list will be accompanied by general notes and disclaimers as outlined in Annex 1. In this connection, it should be noted that inclusion in the EUAL list does not constitute an endorsement, or warranty of the fitness, by WHO of any product for a particular purpose, including in regard to its safety and/or efficacy. The relevant authorities of WHO Member States shall be and remain exclusively responsible for authorizing the use of listed IVDs during a public health emergency in their country.

WHO may, prior to including a product in the list, consult and/or coordinate with relevant NRAs and other parties as appropriate. The validity of an emergency use listing in the context of a public health emergency will generally be for 12 months. All decisions to grant an emergency use listing will be reassessed within 12 months (or sooner, if further data or other information become available that could alter the original opinion). When deemed necessary and warranted based on available data or information, the emergency use listing can be extended. Products may be taken off the EUAL list if new data or information become available that change the safety or performance profile of the product, or immediately upon declaration by the WHO Director-General that there no longer is a PHEIC. Manufacturers are required to supply any new information/data to WHO as soon as it is available.

As WHO is responsible for the EUAL assessment, the ownership of the above mentioned reports lies with WHO. Thus, WHO shall be entitled to use and publish such reports, subject always, however, to the protection of any confidential information of the applicant (i.e. information that is to be considered confidential in accordance with the terms set forth below). Notwithstanding the foregoing, WHO reserves the right to share the full evaluation and inspection reports with the relevant authorities of any interested Member



**EUAL – Vaccines**  
(continued)

could alter the original opinion). When deemed necessary and warranted based on available data and information, the emergency use listing can be extended. Products may be taken off the EUAL list if new data or information become available that change the benefit-risk profile of the product or immediately upon declaration by the WHO Director-General that there no longer is a PHEIC. Manufacturers are required to supply any new information/data to WHO as soon as it is available.

As WHO is responsible for the EUAL assessment, the ownership of the above mentioned reports lies with WHO. Thus, WHO shall be entitled to use and publish such reports, subject always, however, to the protection of any confidential information of the applicant (i.e. information that is to be considered confidential in accordance with the terms set forth below). Notwithstanding the foregoing, WHO reserves the right to share the full evaluation and inspection reports with the relevant authorities of any interested Member State of the Organization and with relevant intergovernmental organizations to the extent possible and appropriate, under obligations of confidentiality.

WHO reserves the right:

- to terminate an assessment, if applicant fails to provide WHO with all the required information.
- to delist a product in case of fraud, misrepresentation, withholding of information by the applicant/manufacturer.

The applicant must inform WHO of any changes/variations regarding the formulation, presentation, methods of manufacture or quality control, specifications, facilities, or any other aspects which might result in a change of safety and/or efficacy/effectiveness of the vaccine.

**Post-emergency-use-listing safety monitoring for vaccines granted EUAL**

Existing international regulatory standards prescribe that marketing

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(continued)

with WHO. Thus, WHO shall be entitled to use and publish such reports, subject always, however, to the protection of any confidential information of the applicant (i.e. information that is to be considered confidential in accordance with the terms set forth below). Notwithstanding the foregoing, WHO reserves the right to share the full evaluation and inspection reports with the relevant authorities of any interested Member State of the Organization and with relevant intergovernmental organizations to the extent possible and appropriate, under obligations of confidentiality.

WHO reserves the right:

- to terminate an assessment, if applicant fails to provide WHO with all the required information.
- to delist a product in case of fraud, misrepresentation, withholding of information by the applicant/manufacturer.

The applicant must inform WHO of any changes/variations regarding the formulation, presentation, methods of manufacture or quality control, specifications, facilities, or any other aspects which might result in a change of safety and/or effectiveness of the medicine.

**Post-emergency-use-listing safety monitoring for medicines granted EUAL**

Existing international regulatory standards prescribe that marketing authorization holders notify national regulatory authorities of adverse events that may cause death or serious deterioration in the health of the patient, user, or another person. This means that users must be encouraged to report all such issues. Those responsible must characterize reports in

**EUAL – Diagnostics**  
(continued)

State of the Organization and with relevant intergovernmental organizations, to the extent possible and appropriate, under obligations of confidentiality.

WHO reserves the right :

- to terminate an assessment, if applicant fails to provide WHO with all the required information.
- to delist a product in case of fraud, misrepresentation, withholding of information by the applicant/manufacturer.

The applicant must inform WHO of any changes/variations to the product, including its design, labelling or manufacture, or to the quality management system, or any other aspects which might affect the safety, quality or performance of the product.

**Post-emergency-use-listing safety monitoring for IVDs granted EUAL**

Existing international regulatory standards prescribe that manufacturers notify national regulatory authorities of adverse events<sup>3</sup> that may cause death or serious deterioration in the state of health of the patient, user, or another person. This means that users must be encouraged to report all quality issues, both administrative and technical, to manufacturers. Manufacturers must characterize complaints in terms of their severity (i.e. serious, moderate, mild) with serious and moderate adverse events to be immediately reported to the relevant national regulatory authorities and WHO. In countries without adequate capacity for this activity, WHO can receive notification of complaints and ensure appropriate evaluation and dissemination of the information.

<sup>3</sup> An adverse event is defined as a product defect (i.e. malfunction or failure, deterioration in characteristics or performance, or inadequacy of labeling or of instructions for use) that, directly or indirectly, has led or might have led to serious medical consequences, namely death or serious deterioration in the state of health of the patient, user or another person.

**EUAL – Vaccines**  
(continued)

authorisation holders notify national regulatory authorities of adverse events following immunization (AEFI). Those events include, in particular, death, hospitalization, or long-term disability. National authorities (regulatory agencies and immunization programs in particular) should also assemble a national database of AEFI. In addition, national authorities should have a mechanism in place that allows manufacturers to be informed about AEFIs related to their products. Similarly, WHO must be informed about all vaccine safety concerns in respect of a vaccine included in the list. The applicant must characterize reports in terms of severity, and immediately report serious AEFIs to the relevant national regulatory authorities and WHO. For reports received by WHO from immunisation programmes or procurement agencies, WHO will inform the respective applicants also to help insure appropriate further investigation.

For vaccines included in the list, appropriate post-EUAL monitoring mechanisms must be established by the applicant to allow for the timely evaluation of adverse events and notification to WHO and the relevant NRAs. This includes ensuring the existence of a spontaneous AEFI reporting system, and the possibility of conducting active surveillance studies in order to investigate specific concerns, either because they were identified as signals during the product clinical evaluation or due to other considerations.

If a safety issue related to a vaccine included in the list cannot be resolved to WHO's satisfaction, WHO reserves the right to revoke the emergency use listing of the product.

**Confidentiality**

WHO will treat all information to which it will gain access as part of the EUAL procedure and which has been marked by the applicant as confidential and proprietary, in

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(continued)

terms of their severity, with serious and unexpected adverse events to be reported immediately to the relevant national regulatory authorities and to WHO. In countries without adequate capacity for this activity, WHO can receive notification of reports and help ensure appropriate evaluation and dissemination of the information.

For EUAL medicines, appropriate post-EUAL monitoring mechanisms must be in place to allow for the timely evaluation of adverse events and notification to WHO and the relevant NRAs.

WHO will ensure that any necessary corrective action is implemented and that users are informed through a safety notice. WHO reserves the right to issue an information notice for users, if at any time, WHO deems that the applicant is not responding to a post-listing safety issue in a timely and scientifically sound manner.

If a safety issue related to a medicine included in the EUAL list cannot be resolved to WHO's satisfaction, WHO reserves the right to revoke the emergency use listing of the product.

**Confidentiality**

WHO will treat all information to which it will gain access as part of the EUAL procedure and which has been marked by the applicant as confidential and proprietary, in accordance with the terms set forth below.

Except as explicitly otherwise provided herein, WHO will take all reasonable measures to ensure:

- that confidential information is not used for any purpose other than as described in this document; and
- that such information is not disclosed or provided to any person who is not bound

**EUAL – Diagnostics**  
(continued)

For IVDs included in the EUAL list, appropriate post-EUAL monitoring mechanisms must be in place to allow for the timely notification and evaluation of adverse events to WHO and the relevant NRAs. The WHO IVD complaint form should be completed as much as possible and sent to WHO. The form is available at the following WHO web address: [http://www.who.int/diagnostics\\_laboratory/postmarket/en/](http://www.who.int/diagnostics_laboratory/postmarket/en/)

WHO will ensure that any necessary field safety corrective action is implemented and that users are informed through a field safety notice. WHO reserves the right to issue an information notice for users, if at any time, WHO deems that the manufacturer is not responding to a complaint in a timely and scientifically sound manner. If a quality issue related to safety or performance cannot be resolved to WHO's satisfaction, WHO reserves the right to revoke the emergency use listing of the product.

**Confidentiality**

WHO will treat all information to which it will gain access as part of the EUAL procedure and which has been marked by the applicant as confidential and proprietary, in accordance with the terms set forth below.

Except as explicitly otherwise provided herein, WHO will take all reasonable measures to ensure:

- that confidential information is not used for any purpose other than as described in this document; and
- that such information is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

WHO will not, however, be bound by any obligations of confidentiality and restrictions on use to the extent it is clearly able to demonstrate that any part of the confidential information: (a). was lawfully in its possession and known to it prior to disclosure by the applicant hereunder, as evidenced by documents antedating the date of disclosure; or

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(continued)*

accordance with the terms set forth below.

Except as explicitly otherwise provided herein, WHO will take all reasonable measures to ensure:

- that confidential information is not used for any purpose other than as described in this document; and
- that such information is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

WHO will not, however, be bound by any obligations of confidentiality and restrictions on use to the extent it is clearly able to demonstrate that any part of the confidential information:

- (a). was lawfully in its possession and known to it prior to disclosure by the applicant hereunder, as evidenced by documents antedating the date of disclosure; or
- (b). was in the public domain or the subject of public knowledge at the time of disclosure hereunder; or
- (c). becomes part of the public domain or the subject of public knowledge through no fault of WHO; or
- (d). becomes available to WHO from a third party not in breach of a legal obligation of confidentiality to the applicant in respect thereof; or
- (e). was subsequently and independently developed by or on behalf of WHO, as shown by written records, by persons who had no knowledge of such Information; or
- (f). is required to be disclosed by law, provided that WHO shall in such case immediately notify the applicant in writing of such obligation and shall provide adequate opportunity to the applicant to object to such disclosure or request confidential treatment thereof (provided always, however, that nothing contained herein shall be construed as a waiver of the privileges and immunities enjoyed by WHO and/or to submit WHO to any national court jurisdiction).

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(continued)*

by similar obligations of confidentiality and non-use as contained herein.

WHO will not, however, be bound by any obligations of confidentiality and restrictions on use to the extent it is clearly able to demonstrate that any part of the confidential information:

- (a). was lawfully in its possession and known to it prior to disclosure by the applicant hereunder, as evidenced by documents antedating the date of disclosure; or
- (b). was in the public domain or the subject of public knowledge at the time of disclosure hereunder; or
- (c). becomes part of the public domain or the subject of public knowledge through no fault of WHO; or
- (d). becomes available to WHO from a third party not in breach of a legal obligation of confidentiality to the applicant in respect thereof; or
- (e). was subsequently and independently developed by or on behalf of WHO, as shown by written records, by persons who had no knowledge of such Information; or
- (f). is required to be disclosed by law, provided that WHO shall in such case immediately notify the applicant in writing of such obligation and shall provide adequate opportunity to the applicant to object to such disclosure or request confidential treatment thereof (provided always, however, that nothing contained herein shall be construed as a waiver of the privileges and immunities enjoyed by WHO and/or to submit WHO to any national court jurisdiction).

*EUAL – Diagnostics  
(continued)*

- (b). was in the public domain or the subject of public knowledge at the time of disclosure hereunder; or
- (c). becomes part of the public domain or the subject of public knowledge through no fault of WHO; or
- (d). becomes available to WHO from a third party not in breach of a legal obligation of confidentiality to the applicant in respect thereof; or
- (e). was subsequently and independently developed by or on behalf of WHO, as shown by written records, by persons who had no knowledge of such Information; or
- (f). is required to be disclosed by law, provided that WHO shall in such case immediately notify the applicant in writing of such obligation and shall provide adequate opportunity to the applicant to object to such disclosure or request confidential treatment thereof (provided always, however, that nothing contained herein shall be construed as a waiver of the privileges and immunities enjoyed by WHO and/or to submit WHO to any national court jurisdiction).

*EUAL – Vaccines  
(continued)*

**Annex 1**

**NOTES AND DISCLAIMERS**

**EUAL List of candidate vaccines**

**General notes**

- The vaccines included in this list are **investigational** vaccines. They have **not** been granted marketing authorization by a functional regulatory authority. This list is exclusively intended to assist interested UN procurement agencies and Member States in determining the acceptability of using a specific investigational vaccine in the context of a Public Health Emergency of International Concern (PHEIC). The products included in this list have been evaluated based on a minimum set of available quality, safety, and efficacy data, an agreed plan for their further evaluation and a plan for their subsequent prequalification. It is the sole prerogative of national authorities to decide whether or not to allow the emergency use of a candidate vaccine in their country. This list is updated regularly. Investigational vaccines are added to the list as and when (following the voluntary participation by relevant manufacturers) the available data on such products are evaluated and, if necessary, relevant sites are inspected by WHO, and are - at the time of evaluation - found to meet the requirements outlined in the *Emergency Use Assessment and Listing Procedure (EUAL) for candidate vaccines for use in the context of a public health emergency*. WHO cannot in respect of any listed product represent that these requirements will continue to be met. WHO may suspend or remove products from the list based on information that may subsequently become available

*EUAL – Medicines  
(continued)*

**Annex 1**

**NOTES AND DISCLAIMERS**

**EUAL List of candidate medicinal products**

**General notes**

- The medicinal products included in this list are **investigational** medicinal products. They have **not** been granted marketing authorization by a stringent regulatory authority. This list is exclusively intended to assist interested UN procurement agencies and Member States in determining the acceptability of using a specific investigational medicinal product in the context of a Public Health Emergency of International Concern (PHEIC). The products included in this list have been evaluated based on a minimum set of available quality, safety, and efficacy data, an agreed plan for their further evaluation and a plan for their subsequent prequalification. It is the sole prerogative of national authorities to decide whether or not to allow the emergency use of a candidate medicinal product in their country. This list is updated regularly. Investigational medicinal products are added to the list as and when (following the voluntary participation by relevant manufacturers) the available data on such products are evaluated and, if necessary, relevant sites are inspected by WHO, and are - at the time of evaluation - found to meet the requirements outlined in the *Emergency Use Assessment and Listing Procedure (EUAL) for candidate medicines for use in the context of a public health emergency*. WHO cannot in respect of any listed product represent that these requirements will continue to be met. WHO may suspend or remove products from the list based on information that may

*EUAL – Diagnostics  
(continued)*

**Annex 1**

**NOTES AND DISCLAIMERS**

**EUAL List of candidate in vitro diagnostics**

**General notes**

- The in vitro diagnostics included in this list are **investigational** diagnostic products. They have **not** been granted marketing authorization by a stringent regulatory authority. This list is exclusively intended to assist interested UN procurement agencies and Member States in determining the acceptability of using a specific in vitro diagnostic in the context of a Public Health Emergency of International Concern (PHEIC). The products included in this list have been evaluated based on a minimum set of available quality, safety, and efficacy data, an agreed plan for their further evaluation and a plan for their subsequent prequalification. It is the sole prerogative of national authorities to decide whether or not to allow the emergency use of a candidate in vitro diagnostic product in their country. This list is updated regularly. Investigational diagnostic products are added to the list as and when (following the voluntary participation by relevant manufacturers) the available data on such products are evaluated and, if necessary, relevant sites are inspected by WHO, and are - at the time of evaluation - found to meet the requirements outlined in the *Emergency Use Assessment and Listing Procedure (EUAL) for candidate in vitro diagnostics (IVDs) for use in the context of a public health emergency*. WHO cannot in respect of any listed product represent that these requirements will continue to be met. WHO may suspend or remove products from the list



***EUAL – Vaccines  
(continued)***

- to it (including information on failure of the responsible NRA to exercise independent and appropriate regulatory oversight).
- The list is not an exhaustive list of vaccines that may be used in a PHEIC. It reflects those investigational products which have been submitted to WHO for evaluation by interested parties.
  - The fact that certain investigational products and suppliers are not included in the list does not mean that if evaluated, they would not be found to meet the above mentioned standards and operational specifications.
  - Inclusion in the list does not imply any approval by WHO of the products and manufacturing sites in question (which is the sole prerogative of national authorities).
  - This list may not be used by manufacturers and suppliers for commercial or promotional purposes.

**Listing of products in the EUAL list**

- WHO may recognize the emergency evaluation and approval of products by regulatory authorities that apply stringent standards for quality, similar to those recommended by WHO, such as, but not limited to, the US Food and Drug Administration (USFDA), the European Medicines Agency (EMA) and Health Canada (HCnda).

**Suggestions relating to procurement**

- Any interested UN procurement agency and Member States intending to use the EUAL list of investigational vaccines for procurement should ensure that only products from the manufacturing sites mentioned in this list are supplied to it.

***EUAL – Medicines  
(continued)***

- subsequently become available to it.
- The list is not an exhaustive list of medicinal products that may be used in a PHEIC. It reflects those investigational products which have been submitted to WHO for evaluation by interested parties.
  - The fact that certain investigational products and suppliers are not included in the list does not mean that if evaluated, they would not be found to meet the above mentioned requirements.
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**Suggestions relating to procurement**

- Any interested UN procurement agency and Member States intending to use the EUAL list of investigational products for procurement should ensure that only products from the manufacturing sites mentioned in this list are supplied to it.
- Organizations using this list for procurement should perform other aspects of qualification prior to purchasing, such as ensuring financial stability and

***EUAL – Diagnostics  
(continued)***

- based on information that may subsequently become available to it.
- The list is not an exhaustive list of diagnostic products that may be used in a PHEIC. It reflects those investigational products which have been submitted to WHO for evaluation by interested parties.
  - The fact that certain investigational products and suppliers are not included in the list does not mean that if evaluated, they would not be found to meet the above mentioned requirements.
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**Listing of in vitro diagnostics in the EUAL list**

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**Suggestions relating to procurement**

- Any interested UN procurement agency and Member States intending to use the EUAL list of diagnostic products for procurement should ensure that only products from the manufacturing sites mentioned in this list are supplied to it.
- Organizations using this list for procurement should perform other aspects of qualification prior to purchasing, such as

*EUAL – Vaccines  
(continued)*

- Organizations using this list for procurement should perform other aspects of qualification prior to purchasing, such as ensuring financial stability and standing of the supplier, ability to supply the required quantities and other related aspects, including the emergency use approval by national authorities in relevant countries.

**Disclaimer to the WHO EUAL  
List of Candidate Vaccines**

1. Inclusion in this list does not constitute an endorsement of the vaccine products listed. WHO explicitly disclaims any warranty of the fitness of any listed investigational vaccines for a particular purpose, including in regard to its safety and/or efficacy.
2. WHO does not furthermore warrant or represent that:
  - a. the list is complete or error free; and/or that
  - b. the listed investigational products which have been found to meet the requirements outlined in the Emergency Use Assessment and Listing Procedure (EUAL) for candidate vaccines for use in the context of a public health emergency will continue to do so; and/or that
  - c. the investigational products listed have obtained emergency use approval for their specified use or any other use in any country of the world, or that their emergency use is otherwise in accordance with the national laws and regulations of any country, including but not limited to patent laws.
3. In addition, WHO wishes to alert procuring organizations that the improper storage, handling and transportation of vaccines (including investigational vaccines) may

*EUAL – Medicines  
(continued)*

standing of the supplier, ability to supply the required quantities and other related aspects, including the emergency use approval by national authorities in relevant countries.

**Disclaimer to the WHO EUAL  
List of Candidate Medicinal  
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2. WHO does not furthermore warrant or represent that:
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  - b. the listed investigational products which have been found to meet the requirements outlined in the Emergency Use Assessment and Listing Procedure (EUAL) for candidate medicines for use in the context of a public health emergency will continue to do so; and/or that
  - c. the investigational products listed have obtained emergency use approval for their specified use or any other use in any country of the world, or that their emergency use is otherwise in accordance with the national laws and regulations of any country, including but not limited to patent laws.
3. In addition, WHO wishes to alert procuring organizations that the improper storage, handling and transportation of medicinal products (including investigational medicinal products) may affect their quality, efficacy and safety.
4. WHO disclaims any and all liability and responsibility

*EUAL – Diagnostics  
(continued)*

ensuring financial stability and standing of the supplier, ability to supply the required quantities and other related aspects, including the emergency use approval by national authorities in relevant countries.

**Disclaimer to the WHO EUAL  
List of Candidate in vitro  
Diagnostic  
Products**

1. Inclusion in this list does not constitute an endorsement of the diagnostic products listed. WHO explicitly disclaims any warranty of the fitness of any listed investigational product for a particular purpose, including in regard to its safety and/or efficacy.
2. WHO does not furthermore warrant or represent that:
  - a. the list is complete or error free; and/or that
  - b. the listed investigational products which have been found to meet the requirements outlined in the Emergency Use Assessment and Listing Procedure (EUAL) for candidate in vitro diagnostics (IVDs) for use in the context of a public health emergency will continue to do so; and/or that
  - c. the investigational products listed have obtained emergency use approval for their specified use or any other use in any country of the world, or that their emergency use is otherwise in accordance with the national laws and regulations of any country, including but not limited to patent laws.
3. In addition, WHO wishes to alert procuring organizations that the improper storage, handling and transportation of in vitro diagnostic products (including investigational in vitro diagnostic products) may



*EUAL – Vaccines  
(continued)*

affect their quality, efficacy and safety.  
4. WHO disclaims any and all liability and responsibility for any injury, death, loss, damage or other prejudice of any kind whatsoever that may arise as a result of or in connection with the procurement, distribution and use of any investigational product included in the list.

7 July 2015

*EUAL – Medicines  
(continued)*

for any injury, death, loss, damage or other prejudice of any kind whatsoever that may arise as a result of or in connection with the procurement, distribution and use of any investigational product included in the list.

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*EUAL – Diagnostics  
(continued)*

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7 July 2015



# Medicines for women and children

## Quality and availability of selected life-saving reproductive health medicines in developing countries

**The UN Commission on Life-Saving Commodities for Women and Children (UNCoLSC) has identified 13 life-saving commodities that could save the lives of more than 6 million women and children in low-income countries over a five-year period if they were more widely available and used appropriately.**

**The WHO Department of Essential Medicines and Health Products organized two surveys to gain a better understanding of the availability and quality of these products in Member States. An overview of the methodology, findings and recommendations of the two surveys is provided in the annexes.**

### Background

The Every Woman Every Child (EWEC) movement aims to address the major health challenges facing women and children. In 2012 the UN Commission on Life-Saving Commodities for Women and Children (UNCoLSC) identified 13 life-saving commodities that, if more widely accessed and properly used, could save the lives of more than 6 million women and children over a five-year period (1). These commodities include medicines to treat post-partum haemorrhage and eclampsia, injectable antibiotics for neonatal sepsis, antenatal corticosteroids to accelerate lung maturation in premature infants, chlorhexidine for cord care, amoxicillin to treat children with pneumonia, oral rehydration salts and zinc to treat children with diarrhoea, as well as contraceptive implants, emergency contraceptives and condoms.

The Commission recommended 10 time-bound actions to improve access to these commodities in EWEC countries, i.e. the 49 countries of the world with the lowest income. Two of the 10 recommendations are within the normative mandate of WHO: Recommendation 4 on quality strengthening (*“By 2015, at least three manufacturers per commodity are manufacturing and marketing quality-certified and affordable products”*) and Recommendation 5 on regulatory efficiency (*“By 2015, all EWEC countries have standardized and streamlined their registration requirements and assessment processes for the 13 life-saving commodities with support from stringent regulatory authorities, the WHO and regional collaboration”*).

### The surveys

In collaboration with a wide range of stakeholders, the WHO Department

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This article was contributed by: Jitka Šabartová (main researcher for the quality testing survey); Robinah Najjemba (main researcher for the regulation and procurement survey, with Lisa Hedman and Deus Mubangizi), and Monika Zweggarth (editor).

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of Essential Medicines and Health Products organized two surveys aiming to understand the quality and availability of the UNCoLSC-identified commodities in EWE countries:

- a quality control testing survey of a total of 204 samples collected in 10 countries (*Annex 1*); and
- a questionnaire-based online survey on regulation and procurement of the commodities (*Annex 2*).

These are the first surveys of this kind to be conducted since the inception of the UNCoLSC. The full survey reports will be published on the WHO website.

### Main findings

The survey on regulation and procurement found that many countries had the formal structures and procedures required to purchase products and to control their quality, but staff and funding limitations affected their operational efficiency.

Registration coverage was reasonable for most products, although none of 22 respondent countries had all 18 UNCoLSC-recommended products on their registers. There were many brands of most injectable antibiotics, but the choice was much more limited for some other commodities. More than half of the registered products identified in the survey came from India and China; 11% were manufactured locally.

Most UNCoLSC-recommended commodities were being procured; some but not all were tracked by logistics management information systems (LMIS) at least at the central level. In most countries, and for the majority of commodities, at least one stock-out had occurred at the central level during the three years preceding the survey.

The quality control testing survey found that of total of 204 samples, 157

(77%), including all 11 samples of WHO-prequalified products, complied fully with the specifications set for the survey. Of the remaining 47 that failed one or more of the tests, five (2%) had extreme deviations in content and/or dissolution which were likely to affect the therapeutic effect of the product. The criteria to define these deviations were the same as those used in two earlier surveys organized by the WHO Prequalification Team (PQT) (*2, 3*).

Three of the five extreme deviations occurred with oxytocin injection, which also had the highest failure rate overall (14 of 22 samples). On the other hand, no failures at all were found for samples of procaine benzylpenicillin injection (including Fortified Procaine Penicillin), amoxicillin dispersible tablets, zinc tablets, zinc syrup and mifepristone tablets.

The results were analyzed in collaboration with the regulatory authorities of the participating countries. Regulatory action was taken in line with the survey findings, and jointly agreed survey recommendations were adopted.

### Conclusions

While the findings highlight once more the ubiquitous resource constraints in national regulation and procurement systems, they also show that most of the UNCoLSC medicines were available on the markets of EWE countries and that extreme quality deficiencies were relatively rare.

It should be borne in mind that any deviations from specifications most likely indicate problems with adherence to good manufacturing practice (GMP) and other international quality standards in manufacturing operations, or with product formulation. The findings of the quality survey highlight once more the importance of comprehensive, proactive regulatory oversight, including both

dossier assessment and risk-based GMP inspections, to ensure that products are designed and manufactured in such a way that they will consistently meet their specifications. For example oxytocin injections – which had the highest failure rate in the survey – were often found to contain large amounts of related substances. While this could have been at least partly due to inadequate storage and degradation in some of the samples, the sum of oxytocin and related substances was often well above 100% suggesting that there may have been large API overages in manufacture. This practice is not normally acceptable and should have been controlled by regulators during the registration process. Similarly, the presence of visible particles in three of 22 oxytocin samples, as well as some of the failures found with other medicines in this survey, pointed to problems in GMP compliance that should be detected and corrected through regulatory inspections. A full discussion of the findings is provided in the survey report that will be published on the WHO website <sup>1</sup>.

Overall the results of the two surveys show that donor-funded programmes have contributed to bridging the gaps in access to quality-assured medicines for all who need them. In recent years

– largely thanks to WHO-supported initiatives and WHO prequalification – there has also been encouraging progress towards good quality regulatory reviews in line with internationally accepted standards, harmonization of regulatory requirements and collaboration in EWEC countries, for example in Africa (4). The results of the two surveys highlight the importance of continuing this work. They provide valuable feedback to regulators, manufacturers, WHO and the UNCoLSC on remaining gaps in making good quality reproductive health medicines widely available.

## References

- 1 [UN Commission on Life-Saving Commodities For Women And Children - Commissioners' Report](#). Geneva: UNFPA; September 2012.
- 2 WHO. [Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa](#). Geneva, World Health Organization, 2011.
- 3 WHO. [Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union](#). Geneva, World Health Organization, 2011.
- 4 First Scientific Conference on Medicines Regulation in Africa. 2 – 3 December 2013, Johannesburg, South Africa. [Conference report](#).

<sup>1</sup> <http://apps.who.int/prequal/> - [Quality monitoring](#)

## Annex 1: Survey of the quality of medicines identified by the UN Commission on Life-Saving Commodities

### Description of the survey

#### Objectives

Primary: Identify products of good quality already available in selected EWEC countries.

Secondary: Evaluate the quality of target medicines collected at the first level of distribution chain.

#### Method

The survey was organized by the WHO Prequalification Team (WHO PQT) in cooperation with National Medicines Regulatory Authorities. A total of 205 samples of selected medicines from the list of 13 life-saving commodities identified by the UN Commission on Life-Saving Commodities for Women and Children (UNCoLSC) were collected at a total of 82 public, private and NGO sites at the first level of the distribution chain, where the influence of potentially inappropriate storage and transport conditions was considered minimal. The samples were tested in WHO-prequalified laboratories in Germany, Kenya and Belgium according to the monographs of the International Pharmacopoeia (Ph. Int), British Pharmacopoeia (BP), US Pharmacopoeia (USP), or a laboratory-validated method.

**Note:** The survey was not designed to distinguish between substandard and counterfeit products.

#### Survey period

Sample collection: September to November 2013; sample testing: December 2013 to April 2014

Joint debriefing and analysis of survey results: July 2014

#### Participating countries

Burkina Faso, Kenya, Madagascar, Nepal, Nigeria, Tajikistan, Tanzania, Uganda, Vietnam and Zimbabwe.

### Overview of findings

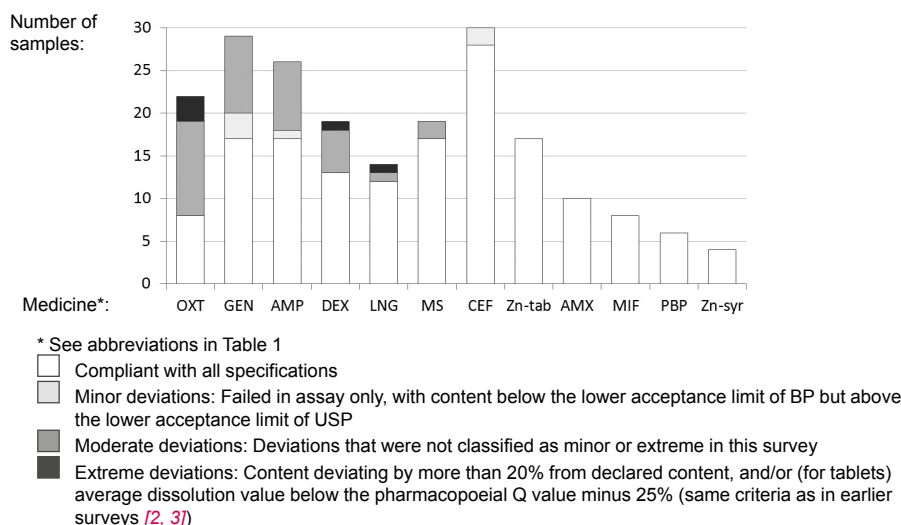
Table 1. Availability of target medicines for sampling

Product	Abbreviation	Countries where sampled	Total samples	Origin			
				India	China	Other imported	Locally manufactured
Oxytocin injection (inj)	OXT	10	22	9	5	8	0
Gentamicin inj	GEN	10	29	8	11	8	2
Ampicillin inj	AMP	10	26	9	12	2	3
Ceftriaxone inj	CEF	10	30	13	10	5	2
Magnesium sulfate inj	MS	9	19	7	1	9	2
Dexamethasone inj	DEX	9	19	6	8	2	3
Levonorgestrel tablets	LNG	8	14	8	0	4	2
Zinc dispersible tablets / syrup	Zn-tab Zn-syr	8	21*	3	0	4	14
Procaine penicillin inj**	PBP	5	6	0	5	1	0
Amoxicillin dispers. tablets	AMX	3	10	5	0	2	3
Mifepristone tablet	MIF	1	8	0	0	0	8
Total			204*	68	52	45	39

**Notes:** \* An additional sample of zinc dispersible tablets was excluded from the survey due to inconclusive testing results. \*\* This included procaine benzylpenicillin injection and procaine benzylpenicillin + benzylpenicillin sodium injection

In each country at least one of the medicines recommended by the UNCoLSC could not be identified for collection. Some medicines were available in different strengths than those recommended by the UNCoLSC (e.g. oxytocin, magnesium sulfate) or in different dosage forms (e.g. amoxicillin). Betamethasone injection was available as an innovator product in some countries, but according to the survey protocol innovator products were excluded from sampling. - The survey outcomes related to the availability of target medicines may underestimate the reality due to the sampling methodology used.

Figure 1. Numbers of compliant samples, and of samples with minor, moderate and extreme deviations



The overall rate of non-compliance with the specifications set for the survey (23%) was quite high. However, the share of extreme deviations from the specifications which most likely impact the therapeutic effect due to the low content of active principle or its limited release from the dosage form was relatively low (2%).

Table 2. Numbers of samples that failed each test

Medicine*:	OXT	GEN	AMP	DEX	LNG	MS	CEF
Total samples tested	22	29	26	19	14	19	30
Total samples failed**	14	12	9	6	2	2	2
Visible particles	3	0	n.p.	0	n/a	0	n.p.
Assay	8 (3)	6	3	5 (1)	0	0	2
Related substances	14	n/a	8	n/a	0	n/a	0
pH	0	2	0	0	n/a	2	0
Extractable volume	0	n.p.	n/a	0	n/a	n.p.	n/a
Uniformity of mass	n/a	n/a	1	n/a	n/a	n/a	0
Water content	n/a	n/a	0	n/a	n/a	n/a	0
Composition of gentamicin	n/a	4	n/a	n/a	n/a	n/a	n/a
Free dexamethasone	n/a	n/a	n/a	3	n/a	n/a	n/a
Dissolution	n/a	n/a	n/a	n/a	2 (1)	n/a	n/a
Content uniformity	n/a	n/a	n/a	n/a	1	n/a	n/a

\* See abbreviations in Table 1. — \*\* Some samples failed more than one test.

Shaded dark grey: The most frequently failed test for each medicine

Shaded light grey: n/a: Not applicable for the respective medicine; n.p.: Not performed

(x) Samples with extreme deviations, included in the numbers of samples that failed each test. Five of 204 samples (2%) had extreme deviations (as defined in the notes to Figure 1):

- Three oxytocin samples (content, of labelled amount: 52.0%; 78.6%; and 0-68.7% in the individual ampoules of an extremely heterogeneous sample)
- One dexamethasone phosphate injection (content: 64.4% of labelled amount)
- One sample of levonorgestrel tablets (average dissolution value: 10% of the labelled API amount)



*Annex 1 - Quality testing survey (continued)**Numbers of locally manufactured and imported samples that failed one or more tests*

**Imported:** 40 of 165 (24%)  
**Locally manufactured:** 7 of 39 (18%)

Among the locally manufactured samples there were no failures for zinc, amoxicillin, ceftriaxone and mifepristone. Minor or moderate deviations were found for magnesium sulfate, gentamicin, ampicillin, dexamethasone and levonorgestrel. There were no extreme deviations (see definition in Figure 1 on page 328).

*Numbers of registered and unregistered samples that failed one or more tests*

**Registered:** 45 of 189 (24%)  
**Unregistered** (donations, special import permits): 2 of 15 (13%)

These findings suggest that donors' and procurement agencies' quality assurance measures are effective.

*Proportion of samples that failed one or more tests in countries*

7%	14–20%	29–35%
Zimbabwe	Tanzania, Tajikistan, Uganda, Nepal	Viet Nam, Burkina Faso, Kenya, Madagascar, Nigeria

In some cases testing according to relatively strict pharmacopoeial specifications may have led to non-compliant findings which would not have occurred if the nationally approved manufacturers' specifications had been used. The findings may reflect market complexity and/or varying levels of regulatory scrutiny and standards enforced in countries. The numbers of samples per country were relatively small, and samples were not collected randomly due to the limited availability of some of the products. The results are therefore not representative of the quality of medicines in the countries participating in the survey.

**Table 3. WHO-prequalified medicines**

Survey-relevant products invited for WHO-prequalification	Number of WHO-prequalified products at the time of the survey	Number of samples collected in the survey	Number of samples that failed one or more tests
Levonorgestrel tablets	4	8	
Zinc dispersible tablets	2	3	<i>Zero</i>
Ceftriaxone injection	4	0	
Dexamethasone injection	1	0	
Oxytocin injection	0	n/a	
Magnesium sulfate injection	0	n/a	

## Recommendations

A complex approach is necessary to improve the availability and quality of UNCoLSC target medicines. Apart from recommendations of a technical nature, the survey participants agreed on the following approaches and recommendations:

*To support demand and promote appropriate use by clinicians:*

- Update therapeutic guidelines and train health care professionals.
- Clearly specify the needed medicines by their dosage form and strength (and API form e.g. salt or base).

*To support efficient regulatory review:*

- Harmonize regulatory requirements and procedures.
- Promote cooperation and information exchange among regulators on post-marketing control (e.g. exchange of assessment and inspection reports, cooperation in sample testing, consultations before adopting regulatory actions against substandard medicines).

*To incentivize manufacturers to register products in EWEC countries:*

- Clearly list needed commodities and possible alternatives to signal the demand to industry.
- Medicines that are relatively easy to produce and control (for example zinc products) can be manufactured locally with pragmatic regulatory requirements.

## Annex 2: Regulation and procurement of life-saving commodities for women and children in Every Woman Every Child (EWEC) countries

### Description of the survey

#### Objectives

- (i) Understand the activities related to the regulation and procurement of the life-saving commodities that contribute to availability and quality medicines in the EWEC countries
- (ii) Describe the barriers to access to the life-saving commodities.

#### Method

Online questionnaire, developed collaboratively across agencies working to support the UNCoLSC recommendations on the basis of existing assessment tools. Structured questionnaires and MS Excel™ sheets were provided to respondents through the WHO "Data Col" online data collection portal.

#### Aspects included in the survey

1. Regulatory environment (16 respondent countries)
2. Registration status of the UNCoLSC-identified commodities (22 respondent countries)
3. Procurement systems and processes (17 respondent countries)
4. Procurement and supply status of the UNCoLSC-identified commodities (11 respondent countries)

#### Survey period

August 2013 to March 2014

#### Participating countries

Afghanistan, Bangladesh, Burkina Faso, Comoros, Democratic Republic of Congo, Ethiopia, Ghana, Guinea, Guinea-Bissau, Kenya, Kyrgyzstan, Lao People's Democratic Republic, Liberia, Madagascar, Malawi, Nepal, Nigeria, Pakistan, Rwanda, Senegal, Sierra Leone, Somalia, Tajikistan, Tanzania, Togo, Uganda, Uzbekistan, Viet Nam, Zambia and Zimbabwe (not all countries responded to all four parts of the survey).

### Overview of findings

#### 1. Regulatory environment

The country / regulatory authority:

	Number of countries:
• Had a national essential medicines list (EML)	15 of 16
• Had a system for registration of medicines	14 of 16
• Assessed dossiers with quality, safety and efficacy data	14 of 16
• Took less than 24 months on average to register a product	14 of 16
• Took less than 12 months on average to register a product	12 of 16
• Had a fast-track system for medicines registration	11 of 16
• Had a system to control importation of medicines	15 of 16
• Required that all imports must correspond to an import license	13 of 16
• Conducted pre- and/or post-shipment inspections	13 of 16
• Had a post market surveillance system	11 of 16
• Had a system for medicines quality complaints reporting	12 of 16
• Had a functional laboratory	13 of 16
• ...that was certified by a standards accreditation body	6 of 16
• ...that was WHO- prequalified	1 of 16

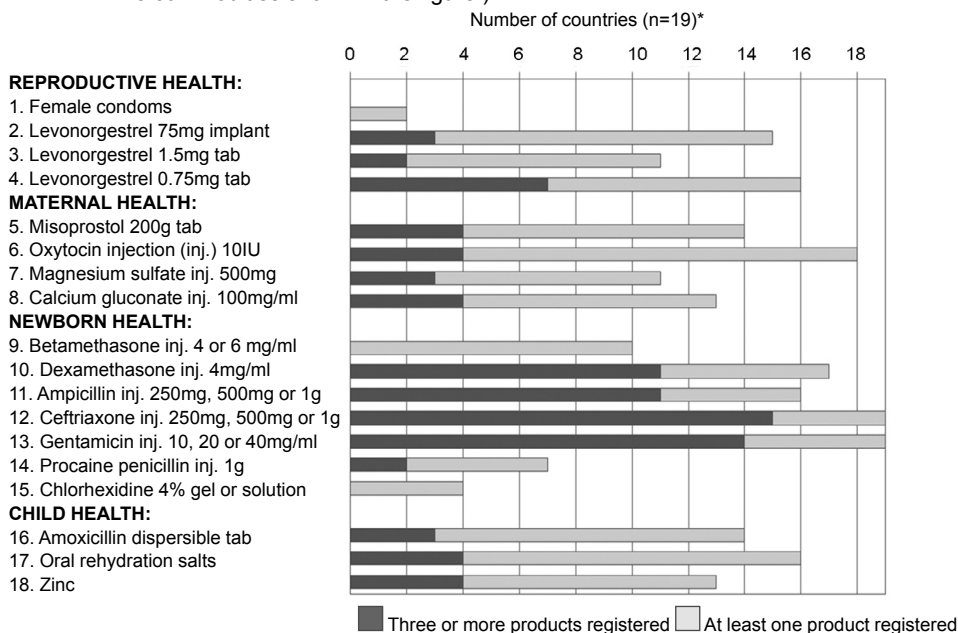
Overall, in terms of regulating the UNCoLSC-identified commodities, the environment was found to be:

<i>Favourable</i>	<i>Partially favourable</i>	<i>Limited</i>
(11-14 of the above criteria met) in Tanzania, Nigeria, Uganda, Ethiopia, Ghana, Liberia, Sierra Leone, Zimbabwe, Bangladesh	(9-10 of the above criteria met) in DRC, Malawi, Senegal, Kyrgyzstan, Rwanda	(2-3 of the above criteria met) in Somalia, Comoros

## Annex 2- Regulation and procurement survey (continued)

## 2. Registration status of the UNCoLSC-identified commodities

**Figure 1. Number of countries that had products of each commodity registered**  
(n=1113 registered products identified in the survey corresponding to the 18 commodities shown in the figure.)



\* Figure 1 excludes Somalia and the Comoros (no registration system) and Sierra Leone (all except one marketing authorization was pending or expired at the time of the survey).

**Total registered products identified in the survey, per country**

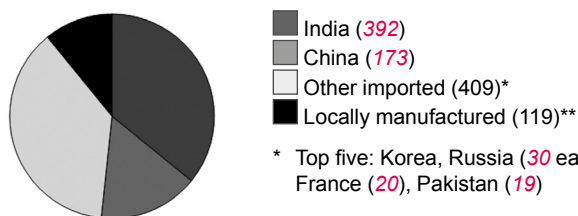
73-133	40-66	11-28
Kyrgyzstan, Nepal, Uganda, Nigeria, Uzbekistan, Viet Nam, Kenya	Ghana, Ethiopia, Zimbabwe, Madagascar, Tanzania, Tajikistan	Guinea, Malawi, Zambia, Burkina Faso, DRC, Senegal

**Number of UNCoLSC-identified commodities with at least one product registered**

14-16 of 18	12-13 of 18	8-11 of 18
Madagascar, Tanzania, Burkina Faso, Zimbabwe, Uganda, Zambia	Malawi, DRC, Nepal, Ethiopia, Uzbekistan, Kenya	Senegal, Tajikistan, Ghana, Guinea, Kyrgyzstan, Nigeria, Viet Nam

**Figure 2: Origin of UNCoLSC-identified products**

(n=1089 products identified in the survey for which the manufacturer and country was known)



\* Top five: Korea, Russia (30 each), Germany (26), Bangladesh (21), France (20), Pakistan (19)

\*\* Top five: Viet Nam (22), Nigeria (21), Kenya (17), Nepal (16), Uzbekistan (14)

*Annex 2 - Regulation and procurement survey (continued)***3. Procurement systems and processes**

For the commodities included in the survey:

Number of countries<sup>†</sup>

- A coordination mechanism existed for procurement and supply management 12 of 17
- The procurement agency followed public procurement policies 16 of 17
- The procurement agency had financial autonomy 14 of 17
- There was a logistics management system (LMIS) for essential commodities 15 of 17
- Evidence of current good manufacturing practice was required for procurement 15 of 17
- A forecasting tool or method was used routinely 14 of 17
- There was an indicator used to track stock-outs at national level 12 of 16
- There were financial/tax incentives for importation of raw materials 6 of 16
- There were financial/tax incentives for finished products 13 of 17

**4. Procurement and supply status of the UNCoLSC-identified commodities**

Respondent countries:	11	11	11	8	8
	Number of countries where each product was:				Countries reporting at least one stock-out at the central level in the three years before the survey** (missing data for some products)
	On the national EML	Included in national policies with the relevant indication	Included in tenders or procurement contracts in the 12 months before the survey	Tracked by LMIS *	
1. Female condoms	5	8	5	8	4 of 6
2. Levonorgestrel implant	6	8	6	6	5 of 5
3. Levonorgestrel 1.5mg	3	4	2	2	1 of 3
4. Levonorgestrel 0.75mg	4	5	4	3	3 of 5
5. Misoprostol	8	8	5	3	0 of 5
6. Oxytocin	11	10	10	7	2 of 9
7. Magnesium sulfate	11	10	9	4	3 of 8
8. Calcium gluconate	10	9	9	6	4 of 8
9. Betamethasone inj	3	3	2	1	1 of 1
10. Dexamethasone inj.	9	8	6	4	2 of 5
11. Ampicillin injection	7	4	4	2	1 of 2
12. Ceftriaxone injection	1	10	10	5	2 of 7
13. Gentamicin injection	11	11	11	7	2 of 8
14. Procaine penicillin	8	8	7	4	2 of 5
15. Chlorhexidine	5	4	4	1	1 of 2
16. Amoxicillin disp. tab	6	8	5	3	3 of 4
17. ORS	11	10	9	5	1 of 7
18. Zinc	10	10	9	5	2 of 6

\* In the respective countries, the national LMIS was reported to be tracking between 7 and 13 of the 18 products included in the survey, although the responses to this section of the survey were often incomplete. Electronic LMIS typically did not extend beyond the central level of the supply chain.

\*\* Six of eight countries that provided data on stock-outs reported at least one stock-out of a survey commodity at the central level at any time during 2010, 2011 or 2012. Products reported to have been out of stock by at least three countries included female condoms, levonorgestrel implant, levonorgestrel 0.75mg tablets, magnesium sulfate injection, calcium gluconate injection and amoxicillin dispersible tablets.

Most stock-outs were for products that were being tracked by the LMIS, suggesting some possible under-reporting in this survey of stock-outs for products that were not being tracked.

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*Annex 2- Regulation and procurement survey (continued)***Recommendations***Regulatory systems*

- Promote regulatory efficiency through joint inspections and dossier reviews, building on existing initiatives, such as those currently coordinated by WHO
- Provide evidence packages for products that are yet unregistered or for which prescription authority changes are under consideration, such as emergency contraceptives and amoxicillin.

*Procurement systems*

- Increase investments in quality monitoring activities commensurately with the increasing number of products on the market
- Promote information-sharing systems (existing or new) on quality complaints, laboratory results and PMS data.

*Registration status of specific life-saving commodities*

- Develop strategies to encourage registration of needed products in EWEC countries, in a South-South collaborative process.

*Procurement status of UNCoLSC-identified products*

- Provide forums where market information is shared and market controls are discussed.
- Align national and partner organizations' quality assurance policies (this may require considerable investment).
- Identify approaches for effective stock management beyond the central supply chain level.
- Ensure continued post-market surveillance especially for commodities such as amoxicillin dispersible tablets and emergency contraceptives that may in future be prescribed by additional categories of health professionals. Model PMS and evidence packages may be useful
- Procurement status of life-saving commodities
- Provide evidence packages to support additions of all UNCoLSC-identified commodities to national EMLs.



# Safety news

## Restrictions

### Repaglinide: contraindicated with clopidogrel

Canada – Health Canada has approved a new contraindication for the anti-diabetic medicine repaglinide (Gluconorm® and generics). Repaglinide must not be administered concomitantly with clopidogrel, a known inhibitor of the CYP2C8 pathway through which repaglinide is predominantly metabolized. Co-administration of repaglinide and clopidogrel may lead to significant decreases in blood glucose levels. The product information for the two medicines is being updated.

► [Health Canada advisory, 31 July 2015.](#)

## Safety warnings

### Sitagliptin, saxagliptin, linagliptin, alogliptin: severe joint pain

United States of America – The US Food and Drug Administration (FDA) has warned that the anti-diabetic medicines sitagliptin, saxagliptin, linagliptin and alogliptin may cause joint pain that can be severe and disabling.

These medicines belong to the class of dipeptidyl peptidase-4 (DPP-4) inhibitors and are approved for treatment of type-2 diabetes. A new warning about this risk has been added to the product information of all FDA-approved products containing a DPP-4 inhibitor.

► [FDA Drug safety communication, 28 August 2015.](#)

### Anagliptin: intestinal obstruction

Japan – Cases of intestinal obstruction have been reported in patients treated with the anti-diabetic anagliptin (Suiny®) in Japan. The Pharmaceutical and Medical Devices Agency (PMDA) has requested updates to the product information to warn about this risk, and to advise caution when using it in patients who have a history of abdominal surgery or intestinal obstruction.

► [PMDA Summary of investigation results, 7 July 2015.](#)

### SGLT2 inhibitors: atypical diabetic ketoacidosis

European Union, New Zealand, Australia – The marketing authorization holders, in consultation with the competent regulatory authorities (1, 2, 3) have advised health professionals to test for raised ketones in patients presenting with acidosis symptoms and treated with a sodium glucose co-transporter 2 (SGLT2) inhibitor, even if plasma glucose levels are near-normal. This follows reports of serious cases of diabetic ketoacidosis associated with SGLT2 inhibitors, including some atypical ones where blood glucose levels were only moderately increased.

SGLT2 inhibitors such as canagliflozin, dapagliflozin and empagliflozin are approved for treatment of type-2 diabetes. They are under review by several



regulatory authorities for their possible association with ketoacidosis (4, 5, 6).

- (1) [MHRA Drug safety update, 26 June 2015.](#)
- (2) [MedSafe safety information; letter to health care professionals, 3 July 2015.](#)
- (3) [TGA Safety advisory, 13 August 2015.](#)
- (4) [FDA Safety announcement, 5 May 2015.](#)
- (5) [EMA News, 12 June 2015.](#)
- (6) [PMDA Risk communication, 21 August 2015.](#)

### **Epoetin beta: possible increased risk of retinopathy in preterm infants**

United Kingdom – The Medicines and Healthcare Products Regulatory Agency (MHRA) has recommended that health professionals should carefully consider the benefits and risks of epoetin beta (NeoRecormon®) in preventing anaemia of prematurity, as a European review has identified a possible risk of retinopathy. More data will be needed to draw a firm conclusion. The product information in the EU will be amended to include this information.

- [Drug Safety Update volume 8 issue 10 May 2015: 3.](#)

### **Adefovir pivoxil: fractures**

Japan – The PMDA has warned about an increased risk of fractures in patients treated with the anti-hepatitis-B medicine adefovir pivoxil (Hepsera®). A total of 43 cases of fractures were reported in Japan during the last three fiscal years; the causal relationship with the fractures was not evaluated. The product information has been updated to warn about this risk and to recommend measures to prevent hypophosphataemia, which can lead to

osteomalacia and can thus increase the risk of fractures.

- [PMDA Summary of investigation results, 7 July 2015.](#)

### **Ingenol mebutate: severe allergic reactions and herpes zoster**

United States of America – The FDA has warned about reports of severe allergic reactions and herpes zoster (shingles) associated with the use of ingenol mebutate gel (Picato®) used to treat actinic keratosis.

Severe eye injuries and skin reactions have also been reported with the use of ingenol mebutate gel. In some of these cases the product was used on larger areas or for a longer period than instructed on the label, or was applied near the mouth, lips or eyes, or was transferred from the hands through application of make-up and insertion of contact lenses.

The FDA is requiring changes to the label to warn about these new safety risks and to provide additional instructions on the safe application of the product.

- [FDA Drug safety communication, 21 August 2015.](#)

### **Asunaprevir, daclatasvir: decreased hepatic residual function**

Japan – The PMDA has warned about cases of decreased hepatic residual function in patients treated with asunaprevir (Sunvepra®) and daclatasvir (Daklinza®) for hepatitis C infection. Patients presented with decreased albumin level, prolonged prothrombin time, ascites and/or hepatic encephalopathy, potentially leading to hepatic failure. In the last three years 21 such cases, including one fatal case, were reported in Japan in which an association with asunaprevir

and daclatasvir combination therapy could not be ruled out. The product information for the two medicines has been revised accordingly.

- [PMDA Investigation results, 7 July 2015](#) and [MHLW Revisions of precautions, 7 July 2015](#).

### **Influenza HA vaccine: optic neuritis**

Japan – The PMDA has requested updates to the product information for four influenza haemagglutinin (HA) vaccine products to reflect the risk of optic neuritis. This follows reports of optic neuritis in people who received this vaccine in Japan, including three cases where causality could not be ruled out.

- [PMDA Summary of investigation results, 7 July 2015](#).

### **Abiraterone acetate: fulminant hepatitis, hepatic failure**

Japan – The PMDA has recommended to revise the package insert of abiraterone tablets (Zytiga®), used to treat castration-resistant prostate cancer, to warn about the risk of fulminant hepatitis and hepatic failure. EMA-approved product information mentions the risk of hepatotoxicity with elevated alanine aminotransferase (ALT), aspartate transaminase (AST) and total bilirubin in patients treated with abiraterone.

- [PMDA Summary of investigation results, 7 July 2015](#).

### **Fingolimod: progressive multifocal leukoencephalopathy**

United States of America – The FDA has updated the product information for fingolimod (Gilenya®) to warn

about a confirmed and a probable case of confirmed progressive multifocal leukoencephalopathy (PML) in patients treated for multiple sclerosis who had not previously received any immunosuppressants (1). PML is a rare and serious brain disease caused by reactivation of the John Cunningham (JC) virus in patients with a weakened immune system.

In April 2015 the EMA and marketing authorization holders had warned health professionals about this risk (2), and the PMDA of Japan has meanwhile started a safety review (3).

- (1) [FDA Drug safety communication, 4 August 2015](#).
- (2) [Drug Safety Update volume 8 issue 10 May 2015: 4](#).
- (3) [PMDA Risk communication, 21 August 2015](#).

### **Methylphenidate patches: permanent skin discolouration**

United States of America – The FDA is warning that permanent loss of skin colour, known as chemical leukoderma, may occur with the use of the methylphenidate transdermal system (Daytrana® patch) to treat attention deficit hyperactivity disorder (ADHD). Chemical leukoderma is not physically harmful but is thought to be irreversible, which may cause emotional distress.

A new warning has been added to the drug label. The FDA is recommending that patients and caregivers should be instructed to watch out for new areas of lighter skin especially under the drug patch, and health care professionals should consider alternative treatments if such changes are reported.

- [FDA Drug safety communication, 24 June 2015](#).

**Diazoxide: pulmonary hypertension**

United States of America – The FDA has warned about a serious lung condition occurring in infants and newborns treated with diazoxide (Proglycem®) for low blood sugar. In all cases, the pulmonary hypertension resolved or improved after diazoxide was stopped. The FDA is investigating this safety issue and will determine whether changes are needed in the product information.

Diazoxide is usually given in the hospital. Health care professionals should closely monitor infants receiving it, especially those with risk factors for pulmonary hypertension, and treatment should be stopped if the condition is identified. Parents and caregivers should be instructed to alert a health professional immediately if they notice signs of difficult breathing in their child.

► [FDA Drug Safety Communication, 16 July 2015.](#)

**General use syringes: not to be used to store medicines**

United States of America – The FDA has warned health care professionals not to administer to patients any compounded or repackaged drugs that have been stored in 3ml and 5ml syringes manufactured by Becton-Dickinson (BD) unless there is no suitable alternative available. Preliminary information indicates that medicines (such as fentanyl, morphine, methadone and atropine) stored in these syringes may lose potency over time due to a possible interaction with the rubber stopper in the syringe.

The syringes have been cleared by the FDA as medical devices for general purpose fluid aspiration and injection only, not for use as a closed container storage system for drug products. This issue may

extend to general use syringes made by other manufacturers. The warning does not extend to products approved by FDA for marketing as pre-filled syringes.

► [FDA Drug alert, 18 August 2015.](#)

**Known risks****Ivabradine: heart problems in patients with angina**

Australia – The Therapeutic Goods Administration (TGA) has completed a safety review of ivabradine (Coralan®), and has recommended measures to reduce the risk of cardiovascular events in patients with angina. Patients who take ivabradine for angina must now have a resting heart rate of at least 70 beats per minute (increased from 60 beats per minute). Ivabradine should not be taken in combination with diltiazem and verapamil, and an existing warning has been strengthened to advise that drinking grapefruit juice should be avoided (rather than 'restricted').

In November 2014 the EMA had recommended similar measures to reduce the risk of heart problems with ivabradine.

► [TGA safety advisory, 9 July 2015.](#)

[EMA. European Medicines Agency recommends measures to reduce risk of heart problems with Corlentor/Procoralan \(ivabradine\). 15 January 2015.](#)

**Indapamide: toxic epidermal necrolysis**

Japan – Following reports of toxic epidermal necrolysis in patient treated with the antihypertensive indapamide (Natrix®, Tenaxil®) in Japan, including a fatal case where a causal relationship could not be ruled out, the PMDA has updated the product information for this medicine to

warn about this risk. Product information in the EU already carries a warning about this adverse reaction, classifying it as very rare.

► [PMDA Summary of investigation results, 7 July 2015.](#)

### NSAIDs: heart attack or stroke

United States of America – The FDA has strengthened its warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, diclofenac and celecoxib, can cause heart attacks or strokes. These events can occur from the first weeks of using an NSAID, and can occur in patients without heart disease or cardiovascular risk factors. The risk may increase with longer use and appears to be greater at higher doses. Patients and health care professionals should remain alert for heart-related side effects for the entire time that NSAIDs are being taken. The FDA is requiring updates to the product information of all prescription NSAIDs, and will also request updates to the over-the-counter non-aspirin NSAID Drug Facts labels. (1)

New Zealand – Medsafe has concluded its consultation on the proposed addition of warning statements on labels of over-the-counter oral and topical diclofenac medicines. The updated statements for oral formulations include warnings about their cardiovascular risks. (2)

► (1) [FDA Drug Safety Communication, 9 July 2015.](#)

(2) [Medsafe News, 19 August 2015.](#)

### Paracetamol: additional measures for safe use

Canada – Based on its review of liver injury and paracetamol (U.S. adopted name: acetaminophen) in Canada, and following strengthened labelling standards introduced in 2009, Health Canada is taking additional steps to improve paracetamol safety.

With over 4 billion doses of paracetamol sold annually, the number of approximately 250 cases of serious liver injury reported each year in Canada can be considered to be relatively low. Over half of the reported cases involved accidental overdose, pointing to a need for clearer warnings. Health Canada will propose a draft revised labelling standard for non-prescription paracetamol-containing products for comment later this year.

► [Health Canada Advisory, 9 July 2015.](#)

### Unchanged recommendations

#### New anti-coagulants: No evidence to support routine blood monitoring

Australia – A recently completed TGA review has found that there is currently no evidence to support a recommendation for routine blood monitoring in patients treated with the new oral anticoagulants apixaban (Eliquis®), dabigatran (Pradaxa®) and rivaroxaban (Xarelto®). Plasma monitoring may be useful in some clinical circumstances, such as overdose or emergency surgery.

The TGA undertook the review following recent publication of articles in the medical literature which suggested that the safety of these medicines could be improved if routine blood monitoring was undertaken.

► [TGA News, 4 June 2015.](#)

## Safety reviews started

Medicine	Use	Concerns	Reviewing authority reference
SGLT2 inhibitors	Treatment of type 2 diabetes	Risk of diabetic ketoacidosis	See page 334
Asunaprevir and daclatasvir combination therapy	Treatment of hepatitis C infection	Risk of thrombocytopenia	► <a href="#">PMDA Risk communication, 21 August 2015.</a>
Human papillomavirus (HPV) vaccines	Prevention of HPV infection; prevention of cervical cancers and various other cancers and conditions caused by HPV	The review does not question that the benefits of HPV vaccines outweigh their risks. It focuses on rare reports of complex regional pain syndrome and postural orthostatic tachycardia syndrome.	► <a href="#">EMA Press release, 13 July 2015.</a>
Codeine	Treatment of cough and cold in children	Potential for serious side effects, including slowed or difficult breathing	► <a href="#">FDA Drug Safety Announcement, 1 July 2015.</a> (EMA review outcomes:) <a href="#">EMA Press release, 24 April 2015</a> (Medsafe review outcomes:) <a href="#">Medsafe Safety information, 29 April 2015.</a>
Gadolinium-based contrast agents	Magnetic resonance imaging (MRI)	Persisting brain deposits after four or more contrast scans	► <a href="#">FDA Drug safety announcement, 27 July 2015.</a>

## WHO Notices of Concern

### Quest Life Sciences

Geneva – Following its inspection of the contract research organization (CRO) Quest Life Sciences Pvt Ltd in October 2014, which revealed some critical and major deviations from good clinical practice and good manufacturing practice, the WHO Prequalification Team (PQT) has published a Notice of Concern about this site (1). Swissmedic has responded by stating that no medicines marketed in or exported from Switzerland have been studied at Quest Life Sciences. (2)

► (1) [WHO Prequalification update, 3 July 2015.](#)

(2) [Swissmedic announcement, 29 July 2015.](#)

### Svizera Labs Pvt Ltd

Geneva – A WHO Notice of Concern has been issued to Svizera Labs Pvt Ltd in India, which has had three anti-tuberculosis medicines prequalified by WHO. The company has been asked to correct several critical and major deviations from good manufacturing practices and data integrity problems observed during a WHO inspection in June 2014.

As with all WHO Notices of Concern, the full text of the request addressed to the company is available on the WHO Prequalification Team's website.

► [Prequalification update, 3 September 2015.](#)



## Falsified product alert

### Falsified diazepam in Central Africa

Geneva – WHO has published a Medical Product Alert about the confirmed circulation of two versions of falsified versions of diazepam tablets circulating in Central Africa.

Since December 2014, over 400 patients in the North East region of the Democratic Republic of Congo (DRC) have suffered from an acute dystonic reaction affecting the muscles of the face, neck and tongue. The adverse effect has resulted in up to 40 hospital admissions per week. So far, all known patients suffering a reaction have recovered.

One of the products has been analysed in the laboratory and was found to contain no diazepam, but between 10mg to 20mg of haloperidol per tablet. Haloperidol is an antipsychotic used primarily for the treatment of schizophrenia, and has a known risk of acute dystonic reactions affecting the face and neck. Without treatment this reaction usually lasts 3 to 4 days, and it sometimes re-occurs. Although all known patients have recovered, the levels of haloperidol present in the tablets pose a serious risk particularly to the young. – A detailed investigation carried out in DRC has revealed that patients had been taking diazepam to treat a wide range of illnesses.

► [WHO Medical Product Alert No. 4/2015, 2 July 2015 \(with photographs\).](#)

The U.S. FDA has warned consumers not to purchase diazepam online due to the potentially serious counterfeiting issue reported in the WHO Medical Product Alert of 2 July 2015.

► [FDA Drug alert, 2 July 2015.](#)

**PRODUCT ONE:** This product is circulating in the Ituri Health District of the Democratic Republic of Congo and the adverse reactions have been focused in the vicinity of Nono. **Laboratory analysis has shown that the product does not contain diazepam, but contains between 10mg to 20mg of haloperidol per tablet. WHO is requesting urgent vigilance for these tablets.**

Stated trade name: **SOLINA**  
 Stated Product: **Diazepam** BP 5 mg  
 Appearance: Light yellow tablets, scored across the centre on one side and **bearing the letters AGOG** on the other side  
 Packaging: Plastic bottle of 1000 tablets stamped in red ink 'Government of Uganda. For public use only, not for sale'.  
 Labelling: Batch Number: SBG038  
 Manufacturing Date: Sep 2014  
 Expiry Date: Aug 2017  
 Stated manufacturer: Centaur Pharmaceuticals

The pharmaceutical manufacturer AGOG has stated that they manufacture haloperidol tablets which are yellow in colour and bear the letters AGOG. However, these are supplied in blisters of 10 tablets and boxes of 10 blisters under the trade name AGOHAL, Haloperidol tablet BP 10mg. AGOG Pharma Ltd have stated that they do not manufacture diazepam.

CENTAUR pharmaceuticals have confirmed that they manufacture diazepam and that the batch number, dates of manufacturing and expiry shown on the falsified packaging correspond to correct existing batch numbers and dates. CENTAUR Pharmaceuticals have stated that they do not manufacture haloperidol. The tablets contained in the plastic bottles and marked AGOG were not manufactured by CENTAUR Pharmaceuticals.

**PRODUCT TWO:** This falsified diazepam product is also circulating in the Democratic Republic of Congo. **The tablets have not yet undergone laboratory analysis, but confirmation has been received that the labelling is falsified. WHO requests increased vigilance for the product.**

Stated trade name: **DIAZPAM TABLETS**  
 Stated Product: **Diazepam** BP 5 mg  
 Appearance: Light yellow tablets, scored across the centre on one side and **bearing the letters AGOG** on the other side  
 Packaging: Container of 1000 tablets  
 Labelling: Batch Number: 2332  
 Manufacturing Date: Nov 2013  
 Expiry Date: Oct 2016  
 Stated manufacturer: Centaur Pharmaceuticals

The pharmaceutical manufacturer AGOG Pharma have confirmed that this packaging and labelling is falsified. AGOG Pharma have confirmed they do not manufacture diazepam.

CENTAUR Pharmaceuticals have confirmed that they manufacture diazepam and that the batch number, date of manufacturing and expiry as shown on the falsified packaging correspond to correct existing batch numbers and dates. The tablets contained in the plastic bottles and marked AGOG were not manufactured by CENTAUR Pharmaceuticals.

# Regulatory news

## Pre-approval processes

### EMA supports development of children's medicines

European Union – The European Medicines Agency (EMA) has launched a one-year pilot to offer free-of-charge meetings with developers of paediatric medicines at an early stage, well before the submission of a paediatric investigation plan (PIP). This strategy is expected to help industry optimize the development plans, ultimately resulting in faster access to children's medicines. The Agency has encouraged interested manufacturers to submit relevant information. During the pilot phase priority will be given to medicines that address major public health needs. (1)

In a separate development the EMA has revised its list of medicines that are not required to submit a paediatric investigation plan (PIP), the so-called class waiver list. The revisions – the most extensive to date – aim to support medicines development for children while avoiding the exposure of children to unnecessary studies. Companies developing medicines that are not covered by the revised list of class waivers should submit a request for a PIP or a product-specific waiver to the EMA's Paediatric Committee (PDCO) for scientific review and agreement. (2)

► (1) [EMA News, 16 June 2015.](#)

(2) [EMA Press release, 23 July 2015.](#)

### TGA implements eCTD submissions

Australia – Pharmaceutical companies can now submit applications for registration of medicines on the Australian Register of Therapeutic Goods to the TGA in the electronic Common Technical Document (eCTD) format. Paper dossiers are no longer required to accompany eCTD formatted submissions. Paper dossiers are also not required to accompany Non-eCTD electronic Submissions (NeeS). Guidance documents are being updated to reflect the changes.

The eCTD format enables a faster, safer and more consistent exchange of information as well as the conduct of electronic review processes for quality, safety and efficacy of medicines. The change to electronic-only submissions follows the successful implementation of a pilot programme in the first six months of 2015.

► [TGA News, 3 July 2015.](#)

### EMA proposes amendments to good clinical practice guidelines

European Union – The EMA has released an addendum to the ICH E6 (R2) guideline on good clinical practice for public consultation.

The amendments take into account the increased cost, scale and complexity of clinical trials since the current guideline was finalized in 1996, as well as developments in technology and risk management processes. The updates are intended to encourage

more efficient approaches to clinical trial design, conduct, oversight, recording and reporting, with updated standards for electronic records and essential documents, while fully preserving the protection of clinical trial participants and data integrity.

The period for comment ends on 3 February 2016.

► [EMA News, 21 August 2015.](#)

### Post-marketing control

#### EMA launches pilot for voluntary post-authorization safety studies

European Union – The EMA has launched a 12-month pilot to encourage companies to seek scientific advice for post-authorization safety studies (PASS) for medicines. This voluntary, optional procedure will help to improve the design of post-marketing safety studies. Its focus is on studies which are not a condition to the marketing authorization.

The new procedure will systematically involve the EMA's pharmacovigilance risk assessment committee (PRAC); two PRAC members will be represented in the Agency's Scientific Advice Working Party (SAWP). The pilot is expected to foster a more integrated approach to the planning of safety, efficacy and quality studies during the lifecycle of a medicine.

► [EMA News, 28 July 2015.](#)

#### Medsafe publishes revised pharmacovigilance guidelines

New Zealand – Medsafe has published the second edition of its Guideline on the Regulation of Therapeutic Products in New Zealand. Part 8: Pharmacovigilance. It has been rewritten and expanded in response to requests for greater clarity

about the circumstances when adverse reaction reporting is required. The new edition includes additional sections on signal management, significant safety issues, safety monitoring documents and safety communications. It incorporates the responses received to the call for comment published in May 2015.

► [Medsafe News, 31 August 2015.](#)

### Antibiotics

#### FDA regulation on use of antibiotics in food-producing animals

United States – The FDA has announced the Veterinary Feed Directive (VFD) final rule, an important piece of the agency's overall strategy to promote the judicious use of antimicrobials in food-producing animals. VFD drugs are veterinary drugs intended for use in or on animal feed that require the supervision of a licensed veterinarian. This strategy will bring the use of VFD drugs under veterinary supervision so that they are used only when necessary for assuring animal health.

The VFD final rule is the third of three core FDA policy documents related to the judicious use of medically important antimicrobial drugs in food-producing animals. It outlines the requirements associated with veterinary authorization, distribution and use of VFD drugs in animal feed. The VFD final rule will become effective on 1 October 2015.

► [FDA News release, 2 June 2015.](#)

## Herbal medicines

### EMA publishes scientific opinions on herbal medicines

European Union – The EMA has started to publish summaries of the recommendations of its Committee on Herbal Medicinal Products (HMPC) on the medicinal uses of a herbal substance in easy to understand, public-friendly language. The information, published on the EMA website, complements the information provided in the package leaflets and is expected to help consumers to make informed choices when using herbal medicines for self-medication.

► [EMA News, 5 August 2015.](#)

## Collaboration

### CFDA joins the ICMRA Interim Management Committee

China – The China Food and Drug Administration (CFDA) has officially joined the Interim Management Committee of the International Coalition of Medicines Regulatory Authorities (ICMRA) and is participating in related work.

The ICMRA is a new executive level global collaboration mechanism for national and regional medicines regulatory authorities. It aims to strengthen strategic planning and to promote regulatory cooperation and regulatory convergence throughout the life-cycle of medicinal products. Making full use of existing guidance and cooperative initiatives, it aims to optimize the capacity and competence building of national and regional medicines regulatory authorities.

The Interim Management Committee of ICMRA currently consists of medicines regulatory authorities from 13 countries and regions, including China, Canada,

Ireland, the United States, Brazil, the European Union, Italy, the Netherlands, Singapore, Japan, Australia, South Africa and the United Kingdom.

► [CFDA News, 26 June 2015.](#)

See also: [The International Coalition of Medicines Regulatory Authorities \(ICMRA\)](#). WHO Drug Information 2015; 29(1): 3-6.

### PMDA publishes 2015 Strategic International Plan

Japan – In response to high domestic and global expectations the Pharmaceuticals and Medical Devices Agency (PMDA) has released its International Strategic Plan 2015 outlining the key international activities envisaged in the coming years. The Agency intends to establish a Regulatory Science Center that will conduct first-in-the-world product reviews, implement safety measures and publish the outcomes. It will also launch the Asian Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs to share its knowledge and experience in product reviews, safety measures, and relief services. Lastly, the PMDA will cooperate with regulatory authorities globally to expand harmonization activities through organizations such as ICH and the International Medical Device Regulators Forum (IMDRF) and work-sharing initiatives for example on GMP and quality management system inspections.

► [PMDA News, 26 June 2015.](#)

### EU and Swiss regulators sign confidentiality arrangement

European and Swiss authorities have agreed to share non-public information on the safety, quality and efficacy of medicines that are already authorized or

under review both in Switzerland and in the EU in order to enhance public health protection. The agreement supports efforts by European and Swiss regulators to improve the oversight of medicines for human and animal health.

► [EMA News, 22 July 2015.](#)

[Swissmedic announcement, 22 July 2015.](#)

### First international generic drug regulators' meeting held

South Africa – The International Generic Drug Regulators Programme (IGDRP) held its first meeting in Pretoria on 27-28 May 2015. Besides the IGDRP members and WHO as an observer, the East African Community Medicines Regulatory Harmonisation initiative and ZAZIBONA, a Southern African group of agencies, were invited to share their work-sharing experiences.

Side meetings were held by the work groups on Active Substance Master File (ASMF)/Drug Master File (DMF) and Biowaivers. The common formats and terminologies developed by the two work groups will not only facilitate collaboration in reviewing generic product applications, but will also enable agencies without a framework to adopt and implement one with minimal resources. Positive feedback was further heard from the information-sharing pilots that are under way since July 2014 using the EU decentralized and centralized procedures as a model.

► [IGDRP Public statement, 23 July 2015.](#)

IGDRP web site: [www.igdrp.com](http://www.igdrp.com)

### Central African countries aim for regulatory harmonization

Republic of the Congo – Six nations of the Central African Economic and Monetary Community (CEMAC) have

resolved to harmonize their regulatory documents, tools and processes.

Regulators from Cameroon, the Central African Republic, Chad, Congo, Equatorial Guinea and Gabon met in Brazzaville on 20-25 July 2015, with WHO technical support and financial support from the EU/ACP/WHO Renewed Partnership, to build their capacity to evaluate medical products. Under the same project, WHO and Organisation for Coordination in the Fight Against Endemic Diseases in Central Africa (OCEAC) are planning other activities for regulatory capacity-building in Central African countries.

► [Essential medicines and health products. Strengthening medicines regulation in Central Africa.](#)

## Law enforcement

### Operation Pangea VIII nets record amount of potentially dangerous products

Regulatory authorities around the world participated in the International Operation Pangea VIII, which took place from 9 to 16 June 2015 as part of the Eighth Annual International Internet Week of Action.

Coordinated by INTERPOL, Operation Pangea is an annual global cooperative effort aiming to combat the unlawful sale and distribution of illegal prescription medicines and medical devices on the Internet. This year's operation involved law enforcement, customs and regulatory authorities from 115 countries. It led to the seizure of a record number of 20.7 million units of potentially dangerous illicit medicines worth US\$ 81 million - more than twice the amount confiscated during the 2013 operation.

► [Interpol News, 18 June 2015.](#)



**Successful Phase III trial****Ebola vaccine shown to be highly effective****Product name:** VSV-EBOV**Developed by:** Public Health Agency of Canada**Licensing agreement:** Merck & Co., Inc and NewLink Genetics Corp, November 2014. Merck assumed responsibility to research, develop, manufacture and distribute the investigational vaccine.**Phase III trial:** The trial is conducted in Guinea and funded by WHO with support from a wide range of partners. It uses a “ring design”, in which the contacts of Ebola cases are vaccinated either immediately or – as an alternative to placebo – three weeks after the identification of an infected patient. To date over 4 000 close contacts of almost 100 Ebola patients, including family members, neighbours and co-workers, have voluntarily participated in the trial.**Findings:** Interim results show 100% efficacy in individuals. The Guinean national regulatory authority and ethics review committee have approved continuation of the trial to obtain more conclusive evidence on the vaccine’s capacity to protect populations through what is called “herd immunity”.**Continuation:** On 26 July 2015 the delayed vaccination arm was discontinued and all contacts were vaccinated immediately after identification of the infected patient. In addition, the trial was extended to include children over 13 years; extension to younger children was to be considered on the basis of new evidence of the vaccine’s safety. On 31 August the ring vaccination trial was extended to Sierra Leone in response to a new case detected there.**Note:** A separate trial of the same vaccine on frontline workers is also being conducted.► [WHO News release, 31 July 2015.](#)**Approved****Rolapitant for chemotherapy-induced nausea and vomiting****Product name:** Varubi®**Dosage form:** Tablets**Class:** P/Neurokinin-1 receptor antagonist**Approval:** FDA**Use:** In combination with other antiemetic agents, to prevent nausea and vomiting associated with emetogenic cancer chemotherapy.**Benefits:** Additional option to prevent delayed phase chemotherapy-induced nausea and vomiting.**Safety information:** Contraindicated with the use of thioridazine (risk of arrhythmias due to increased thioridazine levels).► [FDA News release, 2 September 2015.](#)**Asfotase alfa for rare bone disease****Product name:** Strensiq®**Dosage form:** Subcutaneous injection**Class:** Recombinant fusion protein; first-in-class enzyme replacement therapy to restore alkaline phosphatase function.*ATC code (temporary):* A16AB13**Approval:** EMA marketing authorization under exceptional circumstances; orphan designation. Further safety and efficacy data are being collected.**Use:** Treatment of hypophosphatasia, a rare inherited metabolic disorder affecting the bones. Can be life-threatening when it affects unborn babies or infants, and debilitating when it occurs later in life.**Benefits:** First treatment for this condition; expected to help improve the composition of bones.► [EMA Press release, 26 June 2015.](#)**Cangrelor to prevent blood clotting during surgery****Product name:** EMA: Kengrexal®; U.S.: Kengreal®

## Approved

**Dosage form:** Powder for concentrate for solution for injection / infusion

**Class:** Platelet aggregation inhibitor  
*ATC code:* B01AC25.

**Approval:** EMA (January 2015); FDA (June 2015);

**Use:** To reduce thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) and who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.

**Benefits:** Ability to inhibit platelet aggregation and, co-administered with acetylsalicylic acid, prevent occurrence of thrombotic cardiovascular events, such as heart attack and stent thrombosis, in adults undergoing PCI.

**Safety information:** Serious adverse events include include severe or life-threatening bleeding and hypersensitivity.

► [EMA CHMP Summary of opinion, 22 January 2015.](#)

[FDA News release, 22 June 2015.](#)

### Guanfacin for attention deficit hyperactivity disorder

**Product name:** Intuniv®

**Dosage form:** Prolonged-release tablets

**Class:** Selective alpha2-adrenergic agonist;  
*ATC code:* C02AC02

**Approval:** EMA

**Use:** Treatment of attention deficit hyperactivity disorder (ADHD) in patients aged 6 to 17 years for whom other ADHD medicines are not suitable or tolerated or effective.

**Benefits:** Additional treatment option for ADHD

**Safety information:** Commonly reported serious adverse reactions included hypotension, weight increase, bradycardia and syncope. Risk minimization measures have been put into place, and a

post-authorization long term safety study will be undertaken.

► [EMA Press release, 27 July 2015.](#)

### Valsartan & sacubitril for heart failure

**Product name:** Entresto®

**Dosage form:** Tablets

**Class:** Neprilysin inhibitor (sacubitril) and angiotensin II receptor blocker (valsartan);  
*ATC code (temporary):* C09DX04

**Approval:** FDA (priority review, fast-track designation)

**Use:** Treatment of heart failure in certain patients. Usually administered in conjunction with other heart failure therapies.

**Benefits:** Reduces the rate of cardiovascular death and hospitalization related to heart failure

**Safety information:** Fetal toxicity. When pregnancy is detected, the medicine should be discontinued as soon as possible.

Risk of angioedema, especially in black patients and those with a prior history of angioedema. Patients should be advised to seek emergency medical help immediately if they have symptoms of angioedema or trouble breathing while on treatment.

► [FDA News release, 7 July 2015.](#)

### Alirocumab to lower cholesterol levels

**Product name:** Praluent®

**Dosage form:** Subcutaneous injection

**Class:** Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor, monoclonal antibody

**Approval:** FDA, EMA

**Use:** in addition to diet and maximally tolerated statin therapy, treatment of adult patients with heterozygous familial hypercholesterolemia, and treatment of clinical atherosclerotic cardiovascular disease such as heart attacks or strokes in

patients who require additional lowering of LDL cholesterol.

**Benefits:** Therapy option for patients unable to control high LDL cholesterol levels with currently available treatment.

**Safety information:** Allergic reactions, such as hypersensitivity vasculitis and other serious reactions requiring hospitalization, have been reported with the use of alirocumab.

► [FDA News release, 24 July 2015.](#)

[EMA Press release, 27 July 2015.](#)

### ***Plasmodium falciparum* (malaria) vaccine**

**Product name:** Mosquirix® (RTS,S/AS01)

**Dosage form:** Intramuscular injection, for administration in three doses one month apart, with an additional fourth dose given 18 months later.

**Class:** Malaria vaccine targeting the circumsporozoite protein (CSP) sequence of *Plasmodium falciparum*, combined with the AS01 adjuvant for protection against hepatitis B.

**Approval:** EMA Article 58 procedure, for medicines used outside the EU.

**Use:** Protection against malaria, and protection against hepatitis B in settings that require malaria prevention.

► The vaccine is intended for use in line with official recommendations that take into account the risk of *P. falciparum* malaria in different geographical areas and available malaria control interventions. These recommendations will be defined by the World Health Organization (WHO) and regulatory authorities in the non-EU countries where the vaccine would be used.

**Benefits:** Modest protection against *P. falciparum* malaria in children in the 12 months following vaccination. In a clinical trial conducted in seven African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, Nigeria and Tanzania) the vaccine was effective at

preventing a first or only clinical malaria episode in 56% of children aged between 5-17 months and in 31% of children aged 6-12 weeks. The efficacy of the vaccine decreased after one year. The EMA considered that the benefits of vaccination outweigh the risk in both age groups and may be particularly important in high-transmission areas where mortality is very high.

**Safety information:** The safety profile of the vaccine was considered acceptable.

**Notes:**

- This is the first malaria vaccine to be assessed by a regulatory authority.
- The studies showed that the vaccine does not offer complete protection, and that the protection which it does provide decreases in the longer term. It is therefore important that established protective measures, such as insecticide-treated bed nets, continue to be used in addition to the vaccine.

► [EMA Press release, 24 July 2015.](#)

### **Gefitinib for certain lung cancers**

**Product name:** Iressa®

**Dosage form:** Tablets

**Class:** Protein kinase inhibitor;

ATC code: L01XE02

**Approval:** FDA (orphan product designation)

**Use:** First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors harbour specific types of epidermal growth factor receptor (EGFR) gene mutations, as detected with the *therascreen* EGFR RGQ PCR Kit approved as a companion diagnostic test.

**Benefits:** Additional targeted first-line treatment option for certain lung cancers

**Safety information:** Serious side effects include interstitial lung disease, liver damage, gastrointestinal perforation, severe diarrhea and ocular disorders.

**Notes:** Gefitinib received accelerated FDA approval in 2003 for second-line treatment of patients with advanced NSCLC and was voluntarily withdrawn from the market

## Approved

when confirmatory trials failed to verify clinical benefit in that patient population. Gefitinib was approved by EMA in 2009 for use in patients with the EGFR mutation.

► [FDA News release, 13 July 2015.](#)

**Sonidegib for locally advanced basal cell carcinoma**

**Product name:** Odomzo®

**Dosage form:** Capsule

**Class:** Hedgehog pathway inhibitor;

ATC code: L01XX48

**Approval:** FDA

**Use:** Treatment of locally advanced basal cell carcinoma that has recurred after, or cannot be treated with, surgery or radiation therapy.

**Benefits:** Additional treatment option for advanced basal cell carcinoma that has not spread to other parts of the body.

**Safety information:** May cause death or severe birth defects in a developing fetus when administered to a pregnant women. Can cause serious musculoskeletal-related side effects, including increased serum creatine kinase levels, with rare reports of rhabdomyolysis.

► [FDA News release, 24 July 2015.](#)

**Brexpiprazole for schizophrenia major depressive disorder**

**Product name:** Rexulti®

**Dosage form:** Tablets

**Class:** D2 dopamine partial agonist

**ATC code (temporary):** N05AX16

**Approval:** FDA

**Use:** Treatment of adults with schizophrenia; add-on treatment to an antidepressant medication to treat adults with major depressive disorder

**Benefits:** Reduced occurrence of symptoms of schizophrenia / major depressive disorder, compared to placebo

**Safety information:**

Brexpiprazole is not approved to treat behavioural problems in older people with dementia-related psychosis. An increased risk of death is associated with such off-label use.

Increased risk of suicidal thinking and behaviour in children, adolescents, and young adults taking antidepressants.

Patients should be monitored for these events.

► [FDA News release, 13 July 2015.](#)

**Flibanserin for acquired, generalized female hypoactive sexual desire disorder**

**Product name:** Addyi®

**Dosage form:** Tablets

**Class:** Serotonin 1A receptor agonist and serotonin 2A receptor antagonist

**Approval:** FDA

**Use:** Treatment of acquired, generalized hypoactive sexual desire disorder in premenopausal women.

**Benefits:** About 10 percent more flibanserin-treated patients than placebo-treated patients reported meaningful improvements in satisfying sexual events, sexual desire or distress. Flibanserin has not been shown to enhance sexual performance.

**Safety information:** The product carries a Boxed Warning to highlight the risks of severe hypotension and syncope. These risks are increased in patients drinking alcohol or taking CYP3A4 inhibitors during treatment, and in patients with liver impairment. Flibanserin is contraindicated in these patients. The FDA is requiring additional studies on the serious risks of the interaction between flibanserin and alcohol.

► [FDA News release, 18 August 2015.](#)

Approved

**Lumacaftor & ivacaftor for cystic fibrosis****Product name:** Orkambi®**Dosage form:** Tablets**Class:** Cystic fibrosis transmembrane conductance regulator (CFTR) potentiator  
**ATC code:** R07AX30 (temporary)**Approval:** FDA (orphan drug designation, breakthrough therapy, priority review)**Use:** To treat cystic fibrosis (CF) in patients 12 years and older who have the F508del mutation**Benefits:** Improvement of lung function. First approved drug to treat the cause of cystic fibrosis in people who have two copies of a specific mutation.► [FDA News release, 2 July 2015.](#)**Diagnostic test to differentiate between types of HIV infection****Product name:** Bio-Rad BioPlex 2200®**Use:** Diagnosis of HIV infection**Benefits:** First FDA-approved diagnostic that differentiates between HIV-1 antibodies,

HIV-2 antibodies, and HIV-1 p24 antigen in human serum or plasma specimens. In addition, separate reporting of antigen and antibody detection helps to differentiate between acute and established HIV infection.

► [FDA News release, 23 July 2015.](#)**Additional use approved****Eltrombopag to increase platelet counts in children with rare blood disorder****Product name:** Promacta®**Dosage form:** Tablet**Class:** Systemic haemostatic; **ATC code:** B02BX05**Approval:** FDA (orphan drug designation)**Newly approved use:** Treatment of low platelet counts in children aged one year and older with chronic immune thrombocytopenic purpura (ITP).► [FDA News release, 24 August 2015.](#)

# Publications and events

## Public health

### Special journal issue on vaccine hesitancy

In a special issue of the journal *Vaccine* that was guest-edited by WHO, experts review the role of vaccine hesitancy in limiting vaccine coverage and explore strategies to address it. Vaccine hesitancy refers to delay in acceptance or refusal of safe vaccines despite availability of vaccination services. Globally, one in five children still do not receive routine life-saving immunizations, and an estimated 1.5 million children still die each year of diseases that could be prevented by vaccines that already exist.

Vaccine hesitancy can be caused by many different factors, such as negative beliefs, misinformation, mistrust in health care systems, the role of influential leaders, costs, geographic barriers and concerns about vaccine safety. It is a complex, rapidly changing global problem that occurs in many different settings. The authors note there is no “magic bullet”; tailored strategies and effective communication are key to improving vaccine acceptance.

► [WHO News release, 20 August 2015.](#)

[WHO Recommendations Regarding Vaccine Hesitancy. \*Vaccine\*. 2015;33\(34\):4155-4218. Edited by Melanie Schuster and Philippe Duclos.](#)

### First-ever report on global health service coverage

Geneva – WHO and the World Bank Group have jointly published the first

global monitoring report on health coverage. The report, titled *Tracking universal health coverage*, looked at 37 low- and middle-income countries in 2013. It found that 400 million people did not have access to essential health services and 6% of people were tipped into extreme poverty (\$1.25/day) because of health spending. This percentage rises to 17% if poverty is defined as living on US\$ 2 per day. Across the 37 countries, a median of 1.8% of the population experienced catastrophic health expenditures amounting to more than a quarter of total household spend.

The report further shows that many of the world's most disadvantaged people are missing out on at least one of the most basic services: family planning, antenatal care, skilled birth attendance, child immunization, antiretroviral therapy, tuberculosis treatment, and/or access to clean water and sanitation.

Action is needed in the post-2015 development era to ensure that the world's poor are not left behind. WHO and the World Bank Group recommend that countries should aim to achieve a minimum of 80% population coverage of essential health services, and that everyone everywhere should be protected from catastrophic and impoverishing health payments.

► [Joint WHO/ World Bank new release, 12 June 2015.](#)

World Health Organization, World Bank Group. [Tracking universal health coverage: first global monitoring report.](#) Geneva, Switzerland: WHO, 2015.



## Meningitis C vaccine needed

Geneva – Four international organizations have warned that Africa is at risk of a large meningitis outbreak, and that an acute shortage of meningitis C-containing vaccine threatens to severely limit the world's ability to minimize the number of people affected.

The International Federation of Red Cross and Red Crescent Societies (IFRC), Médecins sans Frontières (MSF), The United Nations Children's Fund (UNICEF), and WHO – which together constitute the International Coordinating Group for Vaccine Provision for Epidemic Meningitis Control (ICG) – have called on manufacturers to step up meningitis C vaccine production by 5 million doses before the start of the next meningitis season in January 2016.

While substantial progress has been made in recent years in protecting Africa from other main sub-types of meningitis with, for example, the introduction of the MenAfrVac vaccine against meningitis A in 2010, much work needs to be done to protect the African meningitis belt from meningitis C outbreaks.

► [WHO News release, 28 July 2015.](#)

## WHO matters

### WHO response to the Ebola interim assessment panel report

Geneva – WHO has welcomed the final report of the interim panel that reviewed the Organization's response to the Ebola outbreak. The panel provided recommendations in three areas: the International Health Regulations, WHO's health emergency response capacity and WHO's role in and cooperation with the wider health and humanitarian systems.

WHO has provided updates on its progress in moving forward in all three areas. Improved ways of working will be incorporated into the ongoing response to end the Ebola outbreak.

► [WHO Statement, 7 July 2015.](#)

## Updated invitations for WHO prequalification

Geneva – The WHO Prequalification Team (PQT), in collaboration with relevant organizations and programmes, has published three updated invitations for expression of interest (EOI) for pre-qualification of medicines. Updated EOIs were posted during July and August 2015 for medicines to treat neglected tropical diseases, influenza-specific antiviral medicines and anti-tuberculosis medicines.

A [combined list](#) of medicines currently invited for prequalification, together with the number of finished products already prequalified and under assessment, is also available on the PQT website.

► WHO PQT. Information and guidelines [web page]. [http://apps.who.int/prequal/info\\_applicants/info\\_for\\_applicants.htm](http://apps.who.int/prequal/info_applicants/info_for_applicants.htm)

## Upcoming events

### Reminder – Joint WHO-UNICEF-UNFPA meeting with manufacturers

The 2015 joint WHO-UNICEF-UNFPA meeting with pharmaceutical and diagnostics manufacturers and suppliers will be held in **Copenhagen on 23-26 November 2015**. Registration is now open.

► [http://apps.who.int/prequal/trainingresources/Meeting\\_Manufacturers2015.htm](http://apps.who.int/prequal/trainingresources/Meeting_Manufacturers2015.htm)

# Consultation documents

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

## *The International Pharmacopoeia*

### Carbamazepinum Carbamazepine

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.608, July 2015).

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

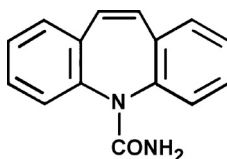
[Note from the Secretariat. It is proposed to revise the monograph on Carbamazepine in *The International Pharmacopoeia*.]

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

**Molecular formula.** C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O

**Relative molecular mass.** 236.3

**Graphic formula.**



**Chemical name.** 5H-Dibenz[b,f]azepine-5-carboxamide; CAS Reg. No. 298-46-4.

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

**Solubility.** Practically insoluble in water; sparingly soluble in acetone; soluble in ethanol (~750 g/L) TS; freely soluble in dichloromethane.

**Category.** Antiepileptic.

**Additional information.** Carbamazepine exhibits polymorphism. The acceptable crystalline form is anhydrous polymorph form III<sup>1</sup>. It corresponds to carbamazepine RS.

**Storage.** Carbamazepine should be kept in a tightly closed container.

## Requirements

**Definition.** Carbamazepine contains not less than 98.0% and not more than 102.0% of  $C_{15}H_{12}N_2O$ , calculated with reference to the dried substance.

### Identity tests

- Either test A or any two of tests B, C and D may be applied.
  - A. Carry out the examination as described under [1.7 Spectrophotometry in the infrared region](#). The infrared absorption spectrum obtained from the test substance without pretreatment is concordant with the spectrum obtained from carbamazepine RS or with the reference spectrum of carbamazepine.
  - 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 gel R6 as the coating substance and a mixture of 78 volumes of toluene R and 22 volumes of methanol R as the mobile phase. Apply separately to the plate 2 µL of each of the following three solutions, prepared using a mixture of equal volumes of ethanol (~750 g/L) TS and dichloromethane R. For solution (A) use 5 mg of the test substance per mL. For solution (B) use 5 mg of carbamazepine RS per mL. For solution (C) use 5 mg of carbamazepine RS and 5 mg of diazepam RS per mL. After removing the plate from the chromatographic chamber allow it to dry in 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 reference solution (C) shows 2 clearly separated spots.
    - B.2 Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using the conditions described under test B.1 but using a plate containing silica gel R5 as the coating substance.

After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium dichromate TS3, then heat it at 105°C for 15 minutes. Examine the chromatogram in daylight.

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 reference solution (C) shows 2 clearly separated spots.
  - C. 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 the retention time of the peak due to carbamazepine in the chromatogram obtained with solution (2).

<sup>1</sup> Adam L Grzesiak, Meidong Lang, Kibum Kim *et al.* Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. Journal of Pharmaceutical Sciences, Vol. 92, No. 11, November 2003.

D. Heat 0.1 g with 2 mL of nitric acid (~1000 g/L) TS in a water-bath for 3 minutes; an orange-red colour is produced.

**Melting range.** 189–193°C.

**Chlorides.** For the preparation of the test solution boil 3.57 g in 50 mL of water for 10 minutes, cool, again adjust the volume, filter. To 25 mL of the filtrate add 10 mL of nitric acid (~130 g/L) TS and proceed as described under [2.2.1 Limit test for chlorides](#); the chloride content is not more than 0.14 mg/g.

**Heavy metals.** Use 1.0 g for the preparation of the test solution as described under [2.2.3 Limit test for heavy metals](#), Procedure 3; determine the heavy metals content according to Method A; not more than 10 µg/g.

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

**Loss on drying.** Dry to constant weight at 105°C; it loses not more than 5.0 mg/g.

**Acidity or alkalinity.** Stir 1.0 g with 20 mL of carbon-dioxide-free water R for 15 minutes and filter. To 10 mL of the filtrate add 0.1 mL of phenolphthalein/ethanol TS and titrate with carbonate-free sodium hydroxide (0.01 mol/L) VS; not more than 0.5 mL is required to obtain a pink colour. Add 0.15 mL of methyl red/ethanol TS and titrate with hydrochloric acid (0.01 mol/L) VS; not more than 1.0 mL is required to obtain a red colour.

**Related substances.** Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the chromatographic conditions given under “Assay, method B”.

Prepare the following solutions. For solution (1) dissolve about 75 mg of the test substance in 25 mL of methanol R, sonicate and dilute to 50 mL with water R. For solution (2) dilute 1 volume of solution (1) to 1000 volumes with a mixture of equal volumes of methanol R and water R. For solution (3) use a solution containing 10 µg of carbamazepine RS and 10 µg of carbamazepine impurity A per mL of a mixture of equal volumes of methanol R and water R.

Inject 20 µL of solution (3). The test is not valid unless the resolution between carbamazepine and carbamazepine impurity A RS is not less than 1.7.

Inject alternately 20 µL each of solution (1) and solution (2). Record the chromatograms for eight times the retention time of carbamazepine. In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to carbamazepine (retention time about 9 minutes): impurity A about 0.9; impurity D about 2.1; and impurity E about 2.5.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.8, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);
- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 2.7, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

- the area of any other impurity peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.10%);
- the sum of the corrected areas of the peaks corresponding to impurity A, impurity D and impurity E and the areas of all other peaks, other than the principal peak, is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (2) (0.05%).

### Assay

- Either method A or B may be applied.
  - Dissolve about 0.1 g, accurately weighed, in sufficient ethanol (~750 g/L) TS to produce 100.0 mL. Dilute 10.0 mL of this solution to 100.0 mL with the same solvent, and again dilute 10.0 mL of this dilution to 100.0 mL with ethanol (~750 g/L) TS. Measure the absorbance (1.6) of a 1 cm layer of the resulting solution at the maximum at about 285 nm. Calculate the percentage content of  $C_{15}H_{12}N_2O$  in the substance being tested, using the absorptivity value of 49.0 ( $A_{1\%}^{1\text{cm}} = 490$ ).
  - 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 cyanopropyl groups (10 µm).<sup>2</sup> As the mobile phase use a mixture of 30 volumes of tetrahydrofuran R, 120 volumes of methanol R, 850 volumes of water R, 0.2 volume of anhydrous formic acid R and 0.5 volume of triethylamine R.

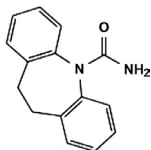
Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 230 nm.

Prepare the following solutions. For solution (1) dissolve about 10 mg of the test substance, accurately weighed, in 25 mL of methanol R, sonicate and dilute to 50.0 mL with water R. For solution (2) use carbamazepine RS to obtain a solution containing 0.2 mg per mL of equal volumes of methanol R and water R.

Inject alternately 20 µL each of solution (1) and (2). The assay is not valid unless the efficiency (N) is at least 5000, determined for the peak due to carbamazepine in the chromatogram obtained with solution (2).

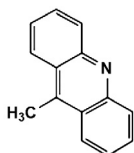
Measure the areas of the peaks corresponding to carbamazepine obtained in the chromatograms from solution (1) and (2) and calculate the percentage content of carbamazepine ( $C_{15}H_{12}N_2O$ ) in the samples using the declared content of  $C_{15}H_{12}N_2O$  in carbamazepine RS.

### Impurities

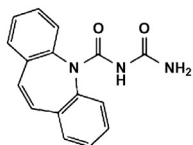


- 10,11-dihydro-dibenzo[b,f]azepine-5-carboxamide (10,11-dihydrocarbamazepine)

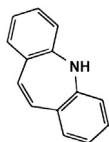
<sup>2</sup> A Nucleosil 100-10 CN column was found suitable.



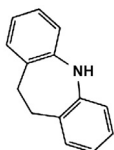
B. 9-methylacridine



C. (5*H*-dibenzo[*b,f*]azepin-5-ylcarbonyl)urea (*N*-carbamoylcarbamazepine)



D. 5*H*-dibenzo[*b,f*]azepine (iminostilbene)



E. 10,11-dihydro-5*H*-dibenzo[*b,f*]azepine (iminodibenzyl)

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## Carbamazepini compressi Carbamazepine tablets

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.632, July 2015).

The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/).

Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: [schmidth@who.int](mailto:schmidth@who.int).

**Category.** Antiepileptic.

**Storage.** Carbamazepine tablets should be kept in a tightly closed container.

**Additional information.** Strength in the current WHO Model List of Essential Medicines (EML): 100 mg, 200 mg. Strength in the current WHO EML for children: 100 mg, 200 mg.

### Requirements

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

**Definition.** Carbamazepine tablets contain not less than 90.0% and not more than 110.0% of the amount of carbamazepine ( $C_{15}H_{12}N_2O$ ) stated on the label.

### Identity tests

- Either test A alone or any two of tests B, C and D may be applied

Transfer a quantity of the powdered tablets equivalent to about 0.25 g of carbamazepine to a 50 mL beaker, add 15 mL of acetone R and boil the solution. Filter while hot, evaporate the filtrate to dryness on a water-bath and dry at 80°C. Dissolve in acetone R, allow to recrystallize and use the crystals for the following tests.

- Carry out the examination with the crystals as described under [1.7 Spectrophotometry in the infrared region](#). The infrared absorption spectrum is concordant with the spectrum obtained from carbamazepine RS or with the reference spectrum of carbamazepine.
- Carry out test B.1 or, where UV detection is not available, test B.2.
  - 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 78 volumes of toluene R and 22 volumes of methanol R as the mobile phase. Apply separately to the plate 2 µL of each of the following three solutions, prepared using as a solvent a mixture of equal volumes of ethanol (~750 g/L) TS and dichloromethane R. For solution (A) use 5 mg of the crystals per mL. For solution (B) use 5 mg of carbamazepine RS per mL. For solution (C) use 5 mg of carbamazepine RS and 5 mg of diazepam RS per mL. After removing the plate from the chromatographic chamber allow it to dry in 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 reference solution (C) shows 2 clearly separated spots.

- B.2 Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using the conditions described under test B.1 but using a plate containing silica gel R5 as the coating substance.

After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium dichromate TS3 then heat the plate at 105°C for 15 minutes. Examine the chromatogram in daylight.

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 reference solution (C) shows 2 clearly separated spots.

- C. 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 the retention time of the peak due to carbamazepine in the chromatogram obtained with solution (2).
- D. Heat 0.1 g of the crystals with 2 mL of nitric acid (~1000 g/L) TS in a water-bath for 3 minutes; an orange-red colour is produced.

**Related substances.** Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions given below under Assay B.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 0.15 g of carbamazepine into a 100 mL volumetric flask, shake with 50 mL of methanol R for about 15 minutes, dilute to volume with water R and filter. For solution (2) dilute 1 volume of solution (1) to 500 volumes with equal volumes of methanol R and water R. For solution (3) use a solution containing 10 µg of carbamazepine RS and 10 µg of carbamazepine impurity A per mL of a mixture of equal volumes of methanol R and water R.

Inject 20 µL of solution (3). The test is not valid unless the resolution between carbamazepine and carbamazepine impurity A RS is not less than 1.7.

Inject alternately 20 µL each of solution (1) and solution (2). Record the chromatograms for four times the retention time of carbamazepine. In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to carbamazepine (retention time about 9 minutes): impurity A about 0.9; impurity D about 2.1; and impurity E about 2.5.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.8, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 2.7, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

**Dissolution.** Carry out the test as described under [5.5 Dissolution test for solid oral dosage forms](#) using as the dissolution medium 900 mL of a 1% solution of sodium dodecyl sulfate R in water and rotating the paddle at 75 revolutions per minute. At 60 minutes withdraw a sample of about 10 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature. Measure the absorbance ([1.6](#)) of a 1 cm layer of the filtered sample, suitably diluted if necessary, at the maximum at about 288 nm.

For each of the tablets tested calculate the amount of carbamazepine ( $C_{15}H_{12}N_2O$ ) in the medium using the absorptivity value of 49.0 ( $A_{1cm}^{1\%} = 490$ ). Evaluate the results as described under [5.5 Dissolution test for solid dosage forms](#), Acceptance criteria.

The amount of carbamazepine in solution for each tablet is not less than 75% (Q) of the amount declared on the label.

### Assay

- Either method A or B may be applied.

- A. Weigh and powder 20 tablets. To an accurately weighed quantity of the powder, containing about 0.06 g of carbamazepine, add 25 mL of ethanol (~750 g/L) TS and boil for a few minutes. Stir the hot mixture in a closed flask for 10 minutes and filter. Wash the flask with ethanol (~750 g/L) TS, filter and dilute the cooled filtrate with sufficient ethanol (~750 g/L) TS to produce 100.0 mL. Dilute 5.0 mL to 250.0 mL with the same solvent.

Measure the absorbance of a 1 cm layer of the solution at the maximum at about 285 nm against a solvent cell containing ethanol (~750 g/L) TS. Calculate the content of  $C_{15}H_{12}N_2O$  using the absorptivity value of 49.0 ( $A_{1cm}^{1\%} = 490$ ).

- 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 cyanopropyl groups (10 µm).<sup>1</sup> As the mobile phase use a mixture of 30 volumes of tetrahydrofuran R, 120 volumes of methanol R, 850 volumes of water R, 0.2 volume of anhydrous formic acid R and 0.5 volume of triethylamine R.

Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 230 nm.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powder equivalent to about 0.1 g of carbamazepine to a 100 mL volumetric flask, add 50 mL of methanol R and sonicate for about 15 minutes. Allow to cool to room temperature, make up to volume with water R and filter the solution. Dilute 10.0 mL of the filtrate to 50.0 mL with a mixture of equal volumes of methanol R and water R. For solution (2) use carbamazepine RS to obtain a solution containing 0.2 mg per mL of equal volumes of methanol R and water R.

Inject alternately 20 µL each of solution (1) and (2). The assay is not valid unless the column efficiency is at least 5000, determined for the peak due to carbamazepine in the chromatogram obtained with solution (2).

Measure the areas of the peaks corresponding to carbamazepine and calculate the content of carbamazepine ( $C_{15}H_{12}N_2O$ ) in the tablets using the declared content of  $C_{15}H_{12}N_2O$  in carbamazepine RS.

**Impurities.** The impurities limited by the requirements of this monograph are impurity A, D and E listed in the monograph for carbamazepine.

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<sup>1</sup> A Nucleosil 100-10 CN column was found suitable.

## *Carbamazepini compressi manducabili* Carbamazepine chewable tablets

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.609, July 2015).

The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/).

Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: [schmidth@who.int](mailto:schmidth@who.int).

**Category.** Antiepileptic.

**Storage.** Carbamazepine chewable tablets should be kept in a tightly closed container.

**Additional information.** Strengths in the current WHO Model List of Essential Medicines (EML): 100 mg, 200 mg. Strengths in the current WHO EML for children: 100 mg, 200 mg.

### Requirements

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

**Definition.** Carbamazepine chewable tablets contain Carbamazepine in a suitable basis that may contain suitable flavouring agents. Carbamazepine chewable tablets contain not less than 90.0% and not more than 110.0% of the amount of carbamazepine ( $C_{15}H_{12}N_2O$ ) stated on the label.

### Identity tests

- Either test A alone or any two of tests B, C and D may be applied

Transfer a quantity of the powdered tablets equivalent to about 0.25 g of carbamazepine to a 50 mL beaker, add 15 mL of acetone R and boil the solution. Filter while hot, evaporate the filtrate to dryness on a water-bath and dry at 80°C. Dissolve in acetone R, allow to recrystallize and use the crystals for the following tests.

- Carry out the examination with the crystals as described under [1.7 Spectrophotometry in the infrared region](#). The infrared absorption spectrum is concordant with the spectrum obtained from carbamazepine RS or with the reference spectrum of carbamazepine.
- Carry out test B.1 or, where UV detection is not available, test B.2.
  - 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 78 volumes of toluene R and 22 volumes of methanol R as the mobile phase. Apply separately to the plate 2 µL of each of the following three solutions, prepared using as a solvent a mixture of equal volumes of ethanol (~750 g/L) TS and dichloromethane R. For solution (A) use 5 mg of the crystals per mL. For solution (B) use 5 mg of carbamazepine RS per mL. For solution (C) use 5 mg of carbamazepine RS and 5 mg of diazepam RS per mL. After removing the plate from the chromatographic chamber allow it to dry in 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 reference solution (C) shows 2 clearly separated spots.

- B.2 Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using the conditions described under test B.1 but using a plate containing silica gel R5 as the coating substance.

After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium dichromate TS3 then heat the plate at 105°C for 15 minutes. Examine the chromatogram in daylight.

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 reference solution (C) shows 2 clearly separated spots.

- C. 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 the retention time of the peak due to carbamazepine in the chromatogram obtained with solution (2).
- D. Heat 0.1 g of the crystals with 2 mL of nitric acid (~1000 g/L) TS in a water-bath for 3 minutes; an orange-red colour is produced.

**Related substances.** Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions given below under Assay B.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 0.15 g of carbamazepine into a 100 mL volumetric flask, shake with 50 mL of methanol R for about 15 minutes, dilute to volume with water R and filter. For solution (2) dilute 1 volume of solution (1) to 500 volumes with equal volumes of methanol R and water R. For solution (3) use a solution containing 10 µg of carbamazepine RS and 10 µg of carbamazepine impurity A per mL of a mixture of equal volumes of methanol R and water R.

Inject 20 µL of solution (3). The test is not valid unless the resolution between carbamazepine and carbamazepine impurity A RS is not less than 1.7.

Inject alternately 20 µL each of solution (1) and solution (2). Record the chromatograms for four times the retention time of carbamazepine. In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to carbamazepine (retention time about 9 minutes): impurity A about 0.9; impurity D about 2.1; and impurity E about 2.5.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.8, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 2.7, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

**Dissolution.** Carry out the test as described under [5.5 Dissolution test for solid oral dosage forms](#) using as the dissolution medium 900 mL of a 1% solution of sodium dodecyl sulfate R in water and rotating the paddle at 75 revolutions per minute. At 60 minutes withdraw a sample of about 10 mL of the medium through an in-line filter. Allow the filtered sample to cool to room

temperature. Measure the absorbance (1.6) of a 1 cm layer of the filtered sample, suitably diluted if necessary, at the maximum at about 288 nm.

For each of the tablets tested calculate the amount of carbamazepine ( $C_{15}H_{12}N_2O$ ) in the medium using the absorptivity value of 49.0 ( $A_{1cm}^{1\%} = 490$ ). Evaluate the results as described under [5.5 Dissolution test for solid dosage forms](#), Acceptance criteria.

The amount of carbamazepine in solution for each tablet is not less than 75% (Q) of the amount declared on the label.

### Assay

- Either method A or B may be applied.

- A. Weigh and powder 20 tablets. To an accurately weighed quantity of the powder, containing about 0.06 g of carbamazepine, add 25 mL of ethanol (~750 g/L) TS and boil for a few minutes. Stir the hot mixture in a closed flask for 10 minutes and filter. Wash the flask with ethanol (~750 g/L) TS, filter and dilute the cooled filtrate with sufficient ethanol (~750 g/L) TS to produce 100.0 mL. Dilute 5.0 mL to 250.0 mL with the same solvent.

Measure the absorbance of a 1 cm layer of the solution at the maximum at about 285 nm against a solvent cell containing ethanol (~750 g/L) TS. Calculate the content of  $C_{15}H_{12}N_2O$  using the absorptivity value of 49.0 ( $A_{1cm}^{1\%} = 490$ ).

- 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 cyanopropyl groups (10 µm).<sup>1</sup> As the mobile phase use a mixture of 30 volumes of tetrahydrofuran R, 120 volumes of methanol R, 850 volumes of water R, 0.2 volume of anhydrous formic acid R and 0.5 volume of triethylamine R.

Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 230 nm.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powder equivalent to about 0.1 g of carbamazepine to a 100 mL volumetric flask, add 50 mL of methanol R and sonicate for about 15 minutes. Allow to cool to room temperature, make up to volume with water R and filter the solution. Dilute 10.0 mL of the filtrate to 50.0 mL with a mixture of equal volumes of methanol R and water R. For solution (2) use carbamazepine RS to obtain a solution containing 0.2 mg per mL of equal volumes of methanol R and water R.

Inject alternately 20 µL each of solution (1) and (2). The assay is not valid unless the column efficiency is at least 5000, determined for the peak due to carbamazepine in the chromatogram obtained with solution (2).

Measure the areas of the peaks corresponding to carbamazepine and calculate the content of carbamazepine ( $C_{15}H_{12}N_2O$ ) in the tablets using the declared content of  $C_{15}H_{12}N_2O$  in carbamazepine RS.

**Impurities.** The impurities limited by the requirements of this monograph are impurity A, D and E listed in the monograph for carbamazepine.

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<sup>1</sup> A Nucleosil 100-10 CN column was found suitable.



## Carbamazepini suspensionum peroralum Carbamazepine oral suspension

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.610, July 2015).

The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/).

Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: [schmidth@who.int](mailto:schmidth@who.int).

**Category.** Antiepileptic.

**Storage.** Carbamazepine oral suspension should be kept in tightly closed, light-resistant containers, protected from freezing and from excessive heat.

**Additional information.** Strength in the current WHO Model List of Essential Medicines (EML): 100 mg per 5 mL. Strength in the current WHO EML for children: 100 mg per 5 mL.

### Requirements

Complies with the monograph for [Liquid preparations for oral use](#).

**Definition.** Carbamazepine oral suspension is a suspension of Carbamazepine in a suitable vehicle, which may be flavoured. It contains not less than 90.0% and not more than 110.0% of the amount of carbamazepine ( $C_{15}H_{12}N_2O$ ) stated on the label.

### Identity tests

- Either test A alone or any two of tests B, C and D may be applied.

Transfer a quantity of the oral suspension equivalent to about 0.25 g of carbamazepine to a centrifuge tube, centrifuge and wash the precipitate with two quantities of 10 mL of water R. Dissolve the precipitate as completely as possible in 10 mL of dichloromethane R, filter and evaporate the filtrate to dryness in air, dry the residue at 105°C for 30 minutes and use it for the following tests.

- Carry out the examination with the residue as described under [1.7 Spectrophotometry in the infrared region](#). The infrared absorption spectrum is concordant with the spectrum obtained from carbamazepine RS or with the reference spectrum of carbamazepine.
- Carry out test B.1 or, where UV detection is not available, test B.2.
  - 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 78 volumes of toluene R and 22 volumes of methanol R as the mobile phase. Apply separately to the plate 2 µL of each of the following three solutions, prepared using as a solvent in a mixture of equal volumes of ethanol (~750 g/L) TS and dichloromethane R. For solution (A) use 5 mg of the residue per mL. For solution (B) use 5 mg of carbamazepine RS per mL. For solution (C) use 5 mg of carbamazepine RS and 5 mg of diazepam RS per mL. After removing the plate from the chromatographic chamber allow it to dry in 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 reference solution (C) shows 2 clearly separated spots.

- B.2 Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using the conditions described under test B.1 but using a plate containing silica gel R5 as the coating substance.

After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium dichromate TS3 then heat the plate at 105°C for 15 minutes. Examine the chromatogram in daylight.

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 reference solution (C) shows 2 clearly separated spots.

- C. 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 the retention time of the peak due to carbamazepine in the chromatogram obtained with solution (2).
- D. Heat 0.1 g of the residue with 2 mL of nitric acid (~1000 g/L) TS in a water-bath for 3 minutes; an orange-red colour is produced.

**pH value** ([1.13](#)). pH of the oral suspension, 3.5–4.5.

**Related substances.** Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions given below under Assay B.

Prepare the following solutions. For solution (1) shake the oral solution and transfer a quantity of it, containing about 0.2 g of Carbamazepine, into a 100 mL volumetric flask, add 50 mL of methanol R and sonicate for about 15 minutes. Allow the suspension to cool to room temperature and dilute to volume with water R. Centrifuge 10 mL of the suspension. Transfer 5.0 mL of the supernatant to a 10 mL volumetric flask and dilute to volume with equal volumes of methanol R and water R. For solution (2) dilute 1 volume of solution (1) to 500 volumes with equal volumes of methanol R and water R. For solution (3) use a solution containing 10 µg of carbamazepine RS and 10 µg of carbamazepine impurity A per mL of a mixture of equal volumes of methanol R and water R.

Inject 20 µL of solution (3). The test is not valid unless the resolution between carbamazepine and carbamazepine impurity A RS is not less than 1.7.

Inject alternately 20 µL each of solution (1) and solution (2). Record the chromatograms for four times the retention time of carbamazepine. In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to carbamazepine (retention time about 9 minutes): impurity A about 0.9; impurity D about 2.1; and impurity E about 2.5.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.8, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 0.4, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 2.7, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).

### Assay

- Either method A or B may be applied.

- A. Shake the oral solution and transfer an accurately weighed quantity of it, containing about 0.1 g of Carbamazepine, to a 100 mL volumetric flask, add about 50 mL of ethanol (~750g/L) TS and sonicate for about 15 minutes. Allow the suspension to cool to room temperature, dilute with the same solvent to volume and filtrate the solution. Dilute 1.0 mL of the filtrate to a 100.0 mL with ethanol (~750g/L) TS.

Measure the absorbance of a 1 cm layer of the solution at the maximum at about 285 nm against a solvent cell containing ethanol (~750 g/L) TS. Determine the weight per mL (1.3.1) of the oral suspension and calculate the content of  $C_{15}H_{12}N_2O$ , weight in volume, of the oral suspension using the absorptivity value of 49.0 ( $A_{1\text{cm}}^{1\%} = 490$ ).

- 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 cyanopropyl groups (10 µm).<sup>1</sup> As the mobile phase use a mixture of 30 volumes of tetrahydrofuran R, 120 volumes of methanol R, 850 volumes of water R, 0.2 volume of anhydrous formic acid R and 0.5 volume of triethylamine R.

Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 230 nm.

Prepare the following solutions. For solution (1) shake the oral solution and transfer an accurately weighed quantity of it, containing about 200 mg of Carbamazepine, to a 100 mL volumetric flask, add 50 mL of methanol R and sonicate for about 15 minutes. Allow the suspension to cool to room temperature, dilute to volume with water R and filtrate the solution. Dilute 5.0 mL of the filtrate to 50.0 mL with equal volumes of methanol R and water R. For solution (2) use carbamazepine RS to obtain a solution containing 0.2 mg per mL of equal volumes of methanol R and water R.

Inject alternately 20 µL each solution (1) and (2). The assay is not valid unless the column efficiency is at least 5000, determined for the peak due to carbamazepine in the chromatogram obtained with solution (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). Determine the weight per mL (1.3.1) of the oral suspension and calculate the content of carbamazepine ( $C_{15}H_{12}N_2O$ ), weight in volume, of the oral suspension using the declared content of  $C_{15}H_{12}N_2O$  in carbamazepine RS.

**Impurities.** The impurities limited by the requirements of this monograph are impurity A, D and E listed in the monograph for carbamazepine.

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<sup>1</sup> A Nucleosil 100-10 CN column was found suitable.

## Norethisteronum

### Norethisterone

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.628, July 2015).

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

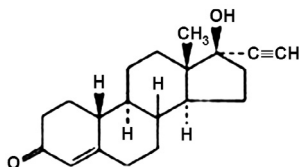
[Note from the Secretariat. It is proposed to revise the monograph on Norethisterone in *The International Pharmacopoeia*.]

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

**Molecular formula.**  $C_{20}H_{26}O_2$

**Relative molecular mass.** 298.4

**Graphic formula.**



**Chemical name.** 17-Hydroxy-19-nor-17 $\alpha$ -pregn-4-en-20-yn-3-one; CAS Reg. No. 68-22-4.

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

**Solubility.** Practically insoluble in water; soluble in methylene chloride, sparingly soluble in acetone and in anhydrous ethanol.

**Category.** Progestational steroid.

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

### Requirements

**Definition.** Norethisterone contains not less than 98.0% and not more than 101.0% of  $C_{20}H_{26}O_2$ , calculated with reference to the dried substance.

### Identity tests

Either test A alone or the tests B, D and E or C, D and E 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 norethisterone RS or with the reference spectrum of norethisterone.

- B. Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using silica gel R1 as the coating substance and a mixture of 95 volumes of dichloromethane R and 5 volumes of methanol R as the mobile phase. Apply separately to the plate 10 µL of each of the following 3 solutions in dehydrated ethanol containing (A) 0.2 mg of the test substance per mL, (B) 0.2 mg of norethisterone RS per mL and (C) 0.2 mg of norethisterone RS and 0.2 mg levonorgestrel RS per mL. Develop the plate. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of air and spray the plate with sulfuric acid/ethanol (10%) TS. Heat the plate to 105°C for 10 minutes, allow it to cool and examine the chromatogram in ultraviolet light (365nm). The principal spot in the chromatogram 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. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions given under “Related substances”. The retention time of the principal peak in the chromatogram obtained from solution (1) is similar to the principal peak in the chromatogram obtained from solution (3).
- D. Dissolve about 10 mg in 1 mL of dehydrated ethanol R. Add silver nitrate (100 g/L) TS and shake; a white precipitate is produced.
- E. Dissolve about 10 mg of the sample in 50 mL of dehydrated alcohol R and dilute to 100.0 mL with the same solvent, dilute 5.0 mL of this solution to 50.0 mL with dehydrated alcohol R. The absorption spectrum ([1.6](#)) of the solution, when observed between 200 nm and 400 nm, exhibits a maximum at about 240 nm; the specific absorbance  $A_{1\text{cm}}^{1\%}$  at 240 nm is between 510 and 630.

**Specific optical rotation** ([1.4](#)). Use a 10 mg per mL solution in acetone R and calculate with reference to the anhydrous substance;  $[\alpha]_{\text{D}}^{20^{\circ}\text{C}} = -32^{\circ}$  to  $-37^{\circ}$ .

**Sulfated ash** ([2.3](#)). Not more than 1.0 mg/g.

**Loss on drying.** Dry to constant weight at 105°C; it loses not more than 5.0 mg/g.

**Related substances.** Carry out the test as described under [1.14.4 High-performance liquid chromatography](#), using a stainless steel column (15 cm × 4.6 mm) packed with end-capped particles of silica gel the surface of which has been modified with chemically-bonded octylsilyl groups (5 µm)<sup>1</sup>.

Use the following conditions for gradient elution:

Mobile phase A: water R;

Mobile phase B: acetonitrile R

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–20	63	37	Isocratic
20–25	63 to 20	37 to 80	Linear gradient
25–35	20	80	Isocratic
35–36	20 to 63	80 to 37	Return to initial composition
36–45	63	37	Re-equilibration

<sup>1</sup> The Agilent ZORBAX Eclipse XDB-C8 column has been found suitable.

Operate with a flow rate of 1.0 mL per minute. As a detector use a variable wavelength spectrophotometer set at a wavelength of 254 nm and, for impurity C, D and I, at 210 nm.

Prepare the following solutions using as the diluent a mixture of 40 volumes of water R and 60 volumes of acetonitrile R. For solution (1) dissolve about 25 mg of the test substance and dilute to 10.0 mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 1.0 mL of this solution to 10.0 mL. For solution (3) dissolve 5.0 mg of norethisterone for system for system suitability RS (containing the impurities A, B, C, D, E, F, G and H) and dilute to 2.0 mL. For solution (4) use a solution containing 2.5 µg of ethinylestradiol RS (impurity I) per mL.

Inject solution 20 µL of solution (3). The assay is not valid unless in the chromatogram recorded at the wavelength of 254 nm the peaks due to impurity B (with a relative retention of about 0.9) and due to norethisterone (retention time about 10 minutes) are baseline separated and the peak-to-valley ratio ( $H_p/H_v$ ) is at least 1.2, where  $H_p$  = height above the baseline of the peak due to impurity A (with a relative retention of about 0.8) and  $H_v$  = the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B.

Inject alternately 20 µL each of solution (1), (2) and (4)

Use the chromatogram obtained with solution (3) and the chromatogram supplied with norethisterone for system suitability RS to identify the peaks due to the impurities A, B, C, D, E, F, G and H. If present, the impurities are eluted at the following relative retention with reference to norethisterone (retention time about 10 minutes): impurity H about 0.3; impurity A about 0.8; impurity B about 0.9; impurity I about 1.1 (at 210 nm); impurity G about 1.5; impurity C about 1.6 (at 210 nm); impurity D about 1.7 (at 210 nm); impurity E about 2.3 and impurity F about 2.4.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.5, is not greater than the area of the principal peak obtained with solution (2) (0.1%);
- the area of any peak corresponding to impurity B is not greater than the area of the principal peak obtained with solution (2) (0.1%);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 0.7, is not greater than 2 times the area of the principal peak obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity F, when multiplied by a correction factor of 1.4, is not greater than the area of the principal peak obtained with solution (2) (0.1%);
- the area of any peak corresponding to impurity H, when multiplied by a correction factor of 1.7, is not greater than 2 times the area of the principal peak obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity G is not greater than 2 times the area of the principal peak obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity C or D, recorded at 210 nm, is not greater than 2 times the area of the principal peak obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity I, recorded at 210 nm, is not greater than the area of the principal peak obtained with solution (4) (0.1%)
- the area of any other peak, other than the principal peak due to norethisterone, is not greater than the area of the principal peak obtained with solution (2) (0.10%);

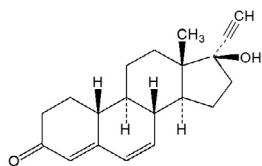


- the sum of the corrected areas of any peak corresponding to impurity A, E, F and H and the areas of all other peaks recorded at 254 nm, other than the principal peak, is not greater than 3 times the area of the principal peak obtained with the solution (2) (0.3 %). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (2) (0.05%).

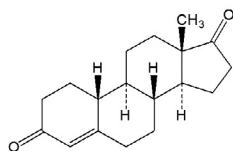
### Assay

Dissolve about 0.20 g, accurately weighed, in 40 mL of tetrahydrofuran R. Add 10 mL of silver nitrate (100 g/L) TS and titrate with sodium hydroxide (0.1 mol/L) VS, determining the end-point potentiometrically. Rinse the electrode with acetone R after each titration. Perform a blank determination and make any necessary correction. 1 mL of 0.1 M sodium hydroxide is equivalent to 29.84 mg of C<sub>20</sub>H<sub>26</sub>O<sub>2</sub>.

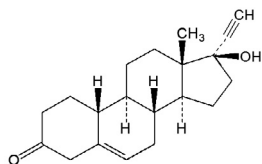
### Impurities



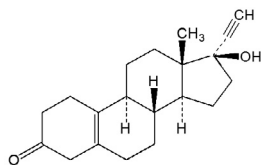
A. 17-hydroxy-19-nor-17 $\alpha$ -pregna-4,6-dien-20-yn-3-one



B. estr-4-ene-3,17-dione (norandrostenedione)

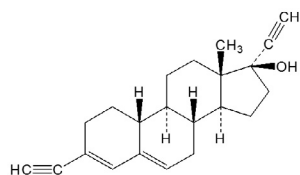


C. 17-hydroxy-19-nor-17 $\alpha$ -pregn-5-en-20-yn-3-one

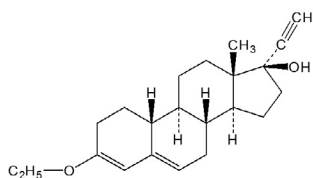


D. 17-hydroxy-19-nor-17 $\alpha$ -pregn-5(10)-en-20-yn-3-one (synthesis impurity<sup>2</sup>)

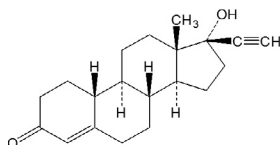
<sup>2</sup> S. Görög, M. Babják, G. Balogh et al.; Estimation of impurity profiles of drugs and related materials, Part 19: Theme with variations. Identification of impurities in 3-oxosteroids; Journal of Pharmaceutical and Biomedical Analysis; 18; (1998); 511-525.



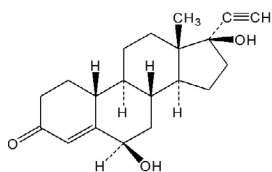
E. 3-ethynyl-19-nor-17 $\alpha$ -pregna-3,5-dien-20-yn-17-ol



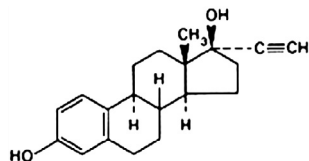
F. 3-ethoxy-19-nor-17 $\alpha$ -pregna-3,5-dien-20-yn-17-ol



G. 17-hydroxy-19-norpregn-4-en-20-yn-3-one (17-epi-norethisterone)



H. 6 $\beta$ ,17-dihydroxy-19-nor-17 $\alpha$ -pregn-4-en-20-yn-3-one (6 $\beta$ -hydroxynorethisterone)  
(degradation product2)



I. 19-Nor-17 $\alpha$ -pregna-1,3,5(10)-trien-20-yne-3,17-diol; 17-ethynyl-estra-1,3,5,(10)-triene-3,17 $\beta$ -diol (ethinylestradiol)

**Reagent to be added:**

Sulfuric acid/ethanol (10%) TS:

**Procedure.** Cool separately 10 mL of sulfuric acid (~1760 g/L) TS and 90 mL of ethanol (~750 g/L) TS to about  $-5^{\circ}\text{C}$ . Carefully add the acid to the ethanol keeping the solution as cool as possible and mix gently.

\*\*\*

## *Norethisteroni compressi* Norethisterone tablets

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.229, June 2015).

The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/).

Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, CH-1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: [schmidth@who.int](mailto:schmidth@who.int).

**Category.** Progestational steroid.

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

**Additional information.** Strengths on the 6<sup>th</sup> invitation to manufacturers of reproductive health products to submit an expression of interest (EOI) for product evaluation to the WHO Prequalification Team - Medicines: 0.35 mg. Additional strengths available 0.625 and 5 mg.

### Requirements

Complies with the monograph on [Tablets](#).

**Definition.** Norethisterone tablets contain not less than 90.0% and not more than 110.0% of the amount of Norethisterone ( $C_{20}H_{26}O_2$ ) stated on the label.

### Identity tests

- Either test A alone or tests B and C may be applied.
- A. Mix a portion of powdered tablets, containing about 50 mg of norethisterone, with 15 mL of hexane R and shake for 15 minutes. Centrifuge the mixture then decant and discard the hexane R. Extract the residue with two 10 mL portions of hexane R, centrifuging, decanting and discarding the supernatant as before. Add 25 mL of dichloromethane to the residue, shake and filter. Evaporate the filtrate to about 3 mL, add a few mL of hexane R to induce crystallization and evaporate to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from norethisterone RS, treated in the same way as the test substance, or with the reference spectrum of norethisterone.
- B. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions given under "Assay", method A. The retention time of the peak due to norethisterone in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).
- C. Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using silica gel R1 as the coating substance and a mixture of 95 volumes of dichloromethane R and 5 volumes of methanol R as the mobile phase. Apply separately to the plate 10 µL of each of the following 3 solutions in dehydrated ethanol R. For solution (A) dissolve a quantity of the powdered tablets, equivalent to about 2 mg of norethisterone, in 10 mL, centrifuge for 10 minutes and use the supernatant liquid. For solution (B) use a solution containing 0.2 mg of norethisterone RS per mL. For solution (C) use a solution containing 0.2 mg of norethisterone RS and 0.2 mg of levonorgestrel RS per mL. Develop the plate. After removing the plate from the chromatographic chamber

allow it to dry in air or in a current of air and spray with sulfuric acid/ethanol (10%) TS. Heat the plate to 105°C for 10 minutes, allow to cool and examine the chromatogram in ultraviolet light (365 nm). The principal spot in the chromatogram 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.

### Dissolution

**For 0.625 mg tablets.** Carry out the test as described under [5.5 Dissolution test for solid oral dosage forms](#) using as the dissolution medium 900 mL of a solution of 0.09% sodium lauryl sulfate R in hydrochloric acid (~3.65 g/L) TS and rotating the paddle at 75 revolutions per minute. At 45 minutes withdraw a sample of 10 mL of the medium through an in-line filter and use the filtrate as solution (1). For solution (2) dissolve a suitable amount of norethisterone RS in 10 mL of ethanol (~750 g/L) TS and dilute to a suitable volume with dissolution medium to obtain a solution containing 0.7 µg per mL.

Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the chromatographic conditions as described under "Assay" but injecting alternately 50 µL each of the solutions (1) and (2).

For each of the six tablets calculate the total amount of norethisterone ( $C_{20}H_{26}O_2$ ), in the medium, using the declared content of ( $C_{20}H_{26}O_2$ ) in norethisterone RS. The amount of norethisterone in solution for each tablet is not less than 80% (Q) of the amount declared on the label.

**For 0.35 mg tablets.** Carry out the test as described above for 0.65 mg tablets but using 500 mL of a solution of 0.09% sodium lauryl sulfate R in hydrochloric acid (~3.65 g/L) TS as the dissolution medium.

### Related substances

Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (15 cm × 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 µm).<sup>1</sup>

Use the following conditions for gradient elution:

Mobile phase A: water R;

Mobile phase B: acetonitrile R

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–20	63	37	Isocratic
20–25	63 to 20	37 to 80	Linear gradient
25–35	20	80	Isocratic
35–36	20 to 63	80 to 37	Return to initial composition
36–45	63	37	Re-equilibration

Operate with a flow rate of 1.0 mL per minute. As a detector use a variable wavelength spectrophotometer set at a wavelength of 254 nm and, for impurity C, D and I at 210 nm.

Prepare the following solutions using as the diluent a mixture of 40 volumes of water R and 60 volumes of acetonitrile R. For solution (1) transfer a quantity of the powdered tablets, containing the equivalent of about 10 mg of norethisterone, in 10 mL and sonicate for

<sup>1</sup> The Agilent ZORBAX Eclipse XDB-C8 column has been found suitable.

15 minutes. Stir vigorously for 15 minutes, centrifuge and use the supernatant. For solution (2) dilute a suitable volume of solution (1) to obtain a solution containing 1.0 µg of norethisterone per mL. For solution (3) dissolve 5.0 mg of norethisterone for system for system suitability RS (containing the impurities A, B, C, D, E, F, G and H) in the solvent and dilute to 2.0 mL. For solution (4) use a solution containing 2.5 µg of ethinylestradiol RS (impurity I) per mL.

Inject solution 20 µL of solution (3). The assay is not valid unless in the chromatogram recorded at the wavelength of 254 nm the peaks due to impurity B (with a relative retention of about 0.9) and due to norethisterone (retention time about 10 minutes) are baseline separated and the peak-to-valley ratio ( $H_p/H_v$ ) is at least 1.2, where  $H_p$  is the height above the baseline of the peak due to impurity A (with a relative retention of about 0.8) and  $H_v$  is the height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B.

Inject alternately 50 µL each of solution (1), (2) and (4).

Use the chromatogram obtained with solution (3) and the chromatogram supplied with norethisterone for system suitability RS to identify the peaks due to the impurities A, B, C, D, E, F, G and H. If present the impurities are eluted at the following relative retention with reference to norethisterone (retention time about 10 minutes): impurity H about 0.3; impurity A about 0.8; impurity B about 0.9; impurity I about 1.1 (at 210 nm); impurity G about 1.5; impurity C about 1.6 (at 210 nm); impurity D about 1.7 (at 210 nm); impurity E about 2.3 and impurity F about 2.4.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 2.5, is not greater than 5 times the area of the principal peak obtained with solution (2) (0.5 %);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 0.7, is not greater than 5 times the area of the principal peak obtained with solution (2) (0.5%);
- the area of any peak corresponding to impurity F, when multiplied by a correction factor of 1.4, is not greater than 5 times the area of the principal peak obtained with solution (2) (0.5%);
- the area of any peak corresponding to impurity H, when multiplied by a correction factor of 1.7, is not greater than 5 times the area of the principal peak obtained with solution (2) (0.5%);
- the area of any peak corresponding to impurity I, recorded at 210 nm, is not greater than 2 times the area of the principal peak obtained with solution (4) (0.5%)
- the area of any other peak, other than the principal peak due to norethisterone, is not greater than 5 times the area of the principal peak obtained with solution (2) (0.5%);

### Assay

- Either method A or B 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 × 4.6 mm), packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl

group ( $5\text{ }\mu\text{m}$ )<sup>2</sup>. As the mobile phase use a mixture of 65 volumes of methanol R and 35 volumes of water R.

Prepare the following solutions using the mobile phase as the diluent. Weigh and powder 20 tablets. For solution (1) transfer a quantity of the powdered tablets, containing about 1.25 mg of norethisterone, accurately weighed, to a 50 mL volumetric flask, add 30 mL mobile phase and sonicate for 15 minutes. Cool to room temperature, dilute to volume and mix. Centrifuge the suspension and use the supernatant. For solution (2) use a solution containing 25  $\mu\text{g}$  of norethisterone 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 244 nm.

Inject alternately 20  $\mu\text{L}$  each of the solutions (1) and (2). Record the chromatograms for about 20 minutes.

Measure the areas of the peak responses obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of norethisterone ( $\text{C}_{20}\text{H}_{26}\text{O}_2$ ) in the tablets, using the declared content of  $\text{C}_{20}\text{H}_{26}\text{O}_2$  in norethisterone RS.

- B. Use the average of the 10 individual results obtained in the test for “Uniformity of content”.

### Uniformity of content

The tablets comply with the test for [5.1 Uniformity of content for single-dose preparations](#) using the following method of analysis.

Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the chromatographic conditions as described under “Assay”, method A.

Prepare the following solutions using the mobile phase as diluent. For solution (1) transfer one tablet to a 25 mL volumetric flask. Add about 15 mL of the diluent, sonicate to disintegrate and shake for 10 minutes and dilute to volume. Centrifuge the suspension and use the clear supernatant liquid. For solution (2) use a solution containing 25  $\mu\text{g}$  of norethisterone RS per mL (for 0.625 mg tablets ) or 14  $\mu\text{g}$  of norethisterone RS per mL (for 0.35 mg tablets).

Inject alternately 20  $\mu\text{L}$  each of solution (1) and (2). Measure the areas of the peaks corresponding to norethisterone obtained in the chromatograms and calculate the content of norethisterone ( $\text{C}_{20}\text{H}_{26}\text{O}_2$ ) in each tablet, using the declared content of  $\text{C}_{20}\text{H}_{26}\text{O}_2$  in norethisterone RS.

### Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph on Norethisterone.

### Reagent to be added:

Sulfuric acid/ethanol (10%) TS

**Procedure.** Cool separately 10 mL of sulfuric acid (~1760 g/L) TS and 90 mL of ethanol (~750 g/L) TS to about  $-5^{\circ}\text{C}$ . Carefully add the acid to the ethanol keeping the solution as cool as possible and mix gently.

\*\*\*

<sup>2</sup> The JADE-PAKODS-AQ (5 Micron 250×4.6mm) column has been found suitable.



## *Dextromethorphani hydrobromidum* Dextromethorphan hydrobromide

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.605/Rev.1, August 2015).

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

*[Note from the Secretariat. It is proposed to revise the monograph on Dextromethorphan hydrobromide.*

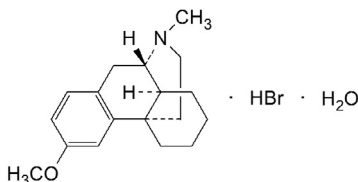
*In investigations leading to the proposed test for related substances it was found that impurity F may co-elute with impurity D. Manufacturers are invited to submit a reference substance of impurity D and to propose a chromatographic method that is capable to separate also the two mentioned impurities.]*

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

**Molecular formula.**  $C_{18}H_{25}NO \cdot HBr \cdot H_2O$

**Relative molecular mass.** 370.3

**Graphic formula**



**Chemical name**

Monohydrate of *ent*-3-methoxy-17-methylmorphinan hydrobromide; (9 $\alpha$ ,13 $\alpha$ ,14 $\alpha$ )-3-methoxy-17-methylmorphinan, hydrobromide, hydrate (1:1:1); (+)-*cis*-6-methoxy-11-methyl-1,3,4,9,10,10a-hexahydro-2*H*-10,4a-(iminoethano)phenanthrene hydrobromide monohydrate; CAS Reg. No. 6700-34-1 (monohydrate).

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

**Solubility.** Sparingly soluble in water; freely soluble in ethanol (~750 g/L) TS.

**Category.** Antitussive.

**Storage.** Dextromethorphan hydrobromide should be kept in a well-closed container, protected from light.

## Requirements

**Definition.** Dextromethorphan hydrobromide contains not less than 99.0% and not more than 101.0% of  $C_{18}H_{25}NO \cdot HBr$ , calculated with reference to the anhydrous substance.

### Identity tests

*[Note from the Secretariat. In the final version of the monograph the order of the different identity tests will be aligned to the style of The International Pharmacopoeia.]*

- Either tests A, E and F or tests B, E, F and G may be applied.
  - A. Dry a small quantity of the test substance for 4 hours under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) over phosphorus pentoxide R and 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 dextromethorphan hydrobromide RS similarly prepared or with the reference spectrum of dextromethorphan hydrobromide.
  - B. The absorption spectrum of a 0.10 mg per mL solution in sodium hydroxide (0.1 mol/L) VS, when observed between 230 nm and 350 nm, exhibits a maximum at 280 nm; the absorbance of a 1 cm layer at this wavelength is about 0.59.
  - E. To a 5 mg per mL solution add 0.25 mL of nitric acid (~130 g/L) TS; this test yields reaction B described under [2.1 General identification tests](#) as characteristic of bromides.
  - F. Determine the specific optical rotation using a 20 mg per mL solution of the test substance in hydrochloric acid (0.1 mol/L) VS. Calculated with reference to the anhydrous substance; the specific optical rotation is between +28.0° to +30.0°.
  - G. Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using silica gel R1 as the coating substance and a freshly prepared mixture of 2 volumes of ammonia (~260 g/L) TS, 10 volumes of dichloromethane R, 13 volumes of methanol R, 20 volumes of ethyl acetate R and 55 volumes of toluene R as the mobile phase. Apply separately to the plate 5 µL of each of the following 2 solutions in methanol R containing (A) 2.5 mg of the test substance per mL and (B) 2.5 mg of dextromethorphan hydrobromide RS per mL. Develop the plate for a distance of about 15 cm. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of air, spray it with potassium iodobismuthate/tartaric acid TS and examine the chromatogram in daylight. The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).

**Sulfated ash** ([2.3](#)). Not more than 1.0 mg/g.

**Water.** Determine as described under [2.8 Determination of water by the Karl Fischer method](#), method A, using about 0.2 g of the substance; the water content is not less than 46 mg/g and not more than 51 mg/g.

**pH value** ([1.13](#)). Dissolve 0.4 g in carbon-dioxide-free water R using gentle heat, dilute to 20 mL with the same solvent and measure the pH at 20°C; the value lies between 5.2 and 6.5.

**Dimethylaniline.** Dissolve 0.5 g in 15 mL of water using gentle heat, cool and add 4 mL of acetic acid (~60 g/L) TS, 1 mL of sodium nitrite (10 g/L) TS and sufficient water to produce 25 mL. Prepare similarly a reference solution containing 5 µg of *N,N*-dimethylaniline R in 25 mL. The colour produced in the test solution is not more intense than that produced

in the reference solution when compared as described under [1.11 Colour of liquids](#); the dimethylaniline content is not more than 10 µg/g.

**Impurity E (Levomethorphan).** 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 cellulose tris(4-methoxybenzoate) groups (5 µm).<sup>1</sup> As the mobile phase use a mixture of 940 volumes of n-hexane R, 60 volumes of 2-propanol R and 1 volume of diethylamine R.

Operate with a flow rate of 0.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 285 nm. Maintain the column at 30°C.

Prepare the following solutions. For solution (1) transfer about 100 mg of the test substance in a 10.0 mL flask. Add 4 mL 2-propanol R, sonicate for about 5 minutes, allow to cool at room temperature and make up to volume with mobile phase. For solution (2) dilute 5.0 mL of solution (1) to 100.0 mL with mobile phase. Dilute 2.0 mL of this solution to 100.0 mL with mobile phase. Prepare solution (3) as indicated in the leaflet of dextromethorphan for system suitability RS (containing a mixture of dextromethorphan and impurity E (levomethorphan)).

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the two principal peaks due to impurity E (levomethorphan) (retention time about 9 minutes) and due to dextromethorphan (relative retention of about 1.3) is at least 3.

Inject alternately 20 µL each of solutions (1) and (2).

In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity E (levomethorphan) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1 %).

**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 octadecylsilyl groups (5 µm).<sup>2</sup>

As the mobile phase use a solution prepared as follows: dissolve 3.11 g of docusate sodium R in a mixture of 400 mL of water R and 600 mL of acetonitrile R, add 0.56 g of ammonium nitrate R and adjust to apparent pH 2.0 with glacial acid R.

Operate with a flow of 1.0 mL per min. As a detector use an ultraviolet spectrophotometer set at a wavelength of 280 nm.

Prepare the following solutions in mobile phase. For solution (1) use a solution containing 1.0 mg of the test substance per mL. For solution (2) dilute 1.0 mL of solution (1) to 200.0 mL. For solution (3) dissolve 2 mg of dextromethorphan impurity A RS in 2 mL of solution (1) and dilute to 25.0 mL.

Inject 20 µL of solution (3). The test is not valid unless the resolution between the peaks due to dextromethorphan (retention time about 22 min) and impurity A (with a relative retention of about 1.1) is at least 1.5.

Inject alternately 20 µL each of solutions (1) and (2). Record the chromatograms for about twice the retention time of dextromethorphan.

<sup>1</sup> A Chiralcel OJ-H column was found suitable.

<sup>2</sup> A Waters Symmetry C18 column was found suitable.

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to dextromethorphan (retention time about 22 minutes): impurity B about 0.4; impurity C about 0.8; impurity D about 0.9; impurity F about 0.9 and impurity A about 1.1.

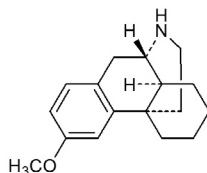
In the chromatogram obtained with solution (1):

- the area of any peak corresponding to either impurity A, impurity B or impurity D/F is not greater than the area of the principal peak obtained with solution (2) (0.5 %);
- the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.2, is not greater than the area of the principal peak obtained with solution (2) (0.5%);
- the area or the corrected area of not more than one peak corresponding to either impurity A, impurity B, impurity C or impurity D/F is greater than 0.5 times the area of the principal peak obtained with solution (2) (0.25 %);
- the area of any other peak, other than the principal peak, is not greater than 0.2 times the area of the principal peak obtained with solution (2) (0.10 %);
- the sum of the corrected area of any peak corresponding to impurity C and the areas of all other peaks, other than the principal peak, is not greater than twice the area of the principal peak obtained with the solution (2) (1.0 %). Disregard any peak with an area less than 0.1 times the area of the principal peak obtained with solution (2) (0.05%).

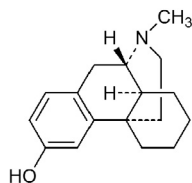
### Assay

Dissolve about 0.3 g, accurately weighed, in a mixture of 5.0 mL of hydrochloric acid (0.1 mol/L) VS and 20 mL of dehydrated ethanol R. Titrate with sodium hydroxide (0.1 mol/L) VS, determining the end-point potentiometrically. Read the volume added between the 2 points of inflexion. Each mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 35.23 mg of  $C_{18}H_{25}NO \cdot HBr$ .

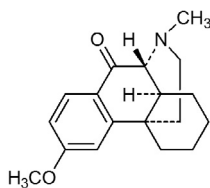
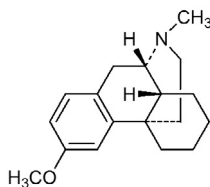
### Impurities



A. *ent*-3-methoxymorphinan (nordextromethorphan) (degradation product),

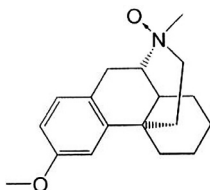


B. *ent*-17-methylmorphinan-3-ol (dextrophan) (degradation product),

C. *ent*-3-methoxy-17-methylmorphinan-10-one (degradation product),D. *ent*-3-methoxy-17-methyl-14 $\alpha$ -morphinan (14-*epi*-dextromethorphan).

[Note from the Secretariat. Graphic formula to be added.]

E. Levomethorphan



F. Dextromethorphan N-Oxide (degradation product)

## Reference substances to be established

Dextromethorphan for system suitability RS

Dextromethorphan impurity A RS

## Reagents to be established

### Potassium iodobismuthate/tartaric acid TS

Stock solution. Suspend 1.7 g of bismuth subnitrate R and 20 g of tartaric acid R in 40 mL of water R. To the suspension add 40 mL of potassium iodide (400 g/L) TS and stir for 1 hour. Filter. The solution may be kept for several days in amber glass bottles.

Spray solution. Mix immediately before use 5 mL of the stock solution with 15 mL of water R.

### Docusate sodium R

Sodium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate.

A commercially available reagent of suitable grade.

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## *Dextromethorphan solutionum peroralem* Dextromethorphan oral solution

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.635, August 2015).

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

*[Note from the Secretariat. It is proposed to include the monograph on Dextromethorphan oral solution in The International Pharmacopoeia.*

*In investigations leading to the proposed test for related substances it was found that impurity F may co-elute with impurity D. Manufacturers are invited to submit a reference substance of impurity D and to propose a chromatographic methods that is capable to separate also the two mentioned impurities.]*

**Category.** Antitussive.

**Storage.** Dextromethorphan oral solution should be kept in well-closed container, protected from light.

**Additional information.** Strength usually available: 15 mg per 10 mL.

### Requirements

Complies with the monograph for [Liquid preparations for oral use](#).

**Definition.** Dextromethorphan oral solution is a solution of Dextromethorphan hydrobromide in a suitable vehicle, which may be flavoured. It contains not less than 90.0% and not more than 110.0% of the amount of Dextromethorphan hydrobromide ( $C_{18}H_{25}NO \cdot HBr \cdot H_2O$ ) stated on the label.

**Manufacture.** The selection of the active ingredient ensures that the oral solution, if tested, would comply with a limit of not more than 0.1% for levomethorphan hydrobromide. A suitable levomethorphan limit test for dextromethorphan oral solutions (and other dextromethorphan finished pharmaceutical products) is published in the Supplementary Information section.

### Identity tests

- Either tests A and B or test B together with any one of tests C or D may be applied.

Transfer a quantity of the oral solution containing about 75 mg of Dextromethorphan hydrobromide to a 250 mL separating funnel, add 20 mL of water R, 5 mL of sodium hydroxide (~100 g/L) TS, 40 mL of hexane R and shake thoroughly. Remove the hexane layer and filter through anhydrous sodium sulfate R into a beaker. Repeat the extraction using two 40 mL portions of hexane R and collecting the extracts in the beaker after filtering. Evaporate the combined extracts and dissolve the residue in 30 mL of dichloromethane R. Use the test solution for "Identity tests" A, B and D.

- A. Evaporate 10 mL of the test solution to dryness and 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



dextromethorphan hydrobromide RS treated similarly or with the reference spectrum of dextromethorphan.

- B. Use 10 mL of the test solution to determine the optical rotation (1.4); the substance is dextrorotatory.
- C. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the same chromatographic conditions as described under "Assay". The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).
- D. 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 2 volumes of ammonia (~260 g/L) TS, 10 volumes of dichloromethane R, 13 volumes of methanol R, 20 volumes of ethyl acetate R and 55 volumes of toluene R as the mobile phase. Apply separately to the plate 5 µL of each of the following three solutions. For solution (A) use the test solution. For solution (B) use about 2.5 mg of dextromethorphan hydrobromide RS per mL of methanol R. For solution (C) use about 2.5 mg of dextromethorphan hydrobromide RS and 2.5 mg of pentoxyverine citrate R per mL of methanol R. After removing the plate from the chromatographic chamber allow it to dry in air. Spray the plate with potassium iodobismuthate TS1 and examine the chromatogram in daylight. 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. The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

**pH value (1.13).** pH of the oral solution, 4.0–6.0.

### Related substances

Carry out the test as described under 1.14.4 High-performance liquid chromatography using the same chromatographic conditions as described under "Assay".

Prepare the following solutions in mobile phase. For solution (1) transfer a volume of the oral solution, equivalent to about 210 mg of Dextromethorphan hydrobromide, into a 200 mL volumetric flask, make up to volume, shake and filter. For solution (2) dilute 2.0 mL of solution (1) to 200.0 mL. For solution (3) use a solution containing about 40 µg of dextromethorphan hydrobromide RS and about 40 µg of dextromethorphan impurity A RS per mL.

Inject 20 µL of solution (3). The test is not valid unless the resolution between the peaks due to dextromethorphan (retention time about 15 min) and impurity A (with a relative retention of about 1.1) is at least 1.5.

Inject alternately 20 µL each of solutions (1) and (2) and record the chromatograms for twice the retention time of dextromethorphan.

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to dextromethorphan (retention time about 22 minutes): impurity B about 0.4; impurity C about 0.8; impurity D/ F about 0.9; and impurity A about 1.1.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to either impurity A, impurity B or impurity D/F is not greater than the 0.5 times the area of the principal peak obtained with solution (2) (0.5 %);

- the area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.2, is not greater than 0.5 times the area of the principal peak obtained with solution (2) (0.5%);

**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 group (5 µm)<sup>1</sup>.

Prepare the mobile phase by dissolving 3.11 g of docusate sodium R in a mixture of 400 mL of water R and 600 mL of acetonitrile R. Add 0.56 g of ammonium nitrate R and adjust to an apparent pH 2.0 with glacial acetic acid R.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 280 nm.

Prepare the following solutions in mobile phase.

For solution (1) transfer a weighed quantity of the oral solution, containing the equivalent of about 37.5 mg of Dextromethorphan hydrobromide, into a 50 mL volumetric flask, make up to volume, shake and filter. For solution (2) use 0.75 mg of dextromethorphan hydrobromide RS per mL.

Inject alternatively 20 µL each of solution (1) and (2) and record the chromatograms.

Measure the areas of the peaks corresponding to dextromethorphan obtained in the chromatograms. Determine the weight per mL ([1.3.1](#)) of the oral solution and calculate the percentage content of Dextromethorphan hydrobromide (C<sub>18</sub>H<sub>25</sub>NO, HBr, H<sub>2</sub>O), weight in volume, of the oral solution, using the declared content of C<sub>18</sub>H<sub>25</sub>NO, HBr in dextromethorphan hydrobromide RS. Each mg of C<sub>18</sub>H<sub>25</sub>NO, HBr is equivalent to 1.0511 mg of C<sub>18</sub>H<sub>25</sub>NO, HBr, H<sub>2</sub>O.

### Impurities

The impurities limited by the requirements of this monograph include impurities A, B, C, D and F listed in the monograph for Dextromethorphan hydrobromide.

### Reagents to be established:

#### Pentoxyverine citrate R

A commercially available reagent of suitable grade.

#### Docusate sodium R

Sodium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate.

A commercially available reagent of suitable grade.

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<sup>1</sup> Shiseido ACR column and Phenomenex Luna column and have been found suitable.

## Levomethorphan limit test for dextromethorphan-containing finished pharmaceutical products

This is a draft proposal for *The International Pharmacopoeia* (Working document QAS/15.636, August 2015).

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

*[Note from the Secretariat. It is proposed to include in the supplementary information section of The International Pharmacopoeia a levomethorphan limit test for dextromethorphan containing finished pharmaceutical products.]*

Dextromethorphan-containing medicines shall contain Dextromethorphan hydrobromide which complies with all the requirements of the respective monograph and other applicable chapters of *The International Pharmacopoeia*. In particular, the concentration of impurity E (levomethorphan) shall not exceed the limit of 0.1% (see monograph on Dextromethorphan hydrobromide).

The following tests allow control laboratories (e.g. national quality control laboratories) to test suspicious dextromethorphan-containing medicines to establish whether or not an active pharmaceutical ingredient (API) meeting the limit for impurity E (levomethorphan) had been used to manufacture the product under examination.

In many cold and cough medicines dextromethorphan is used in combination with other active ingredients, for example, chlorpheniramine, doxylamine, ephedrine, paracetamol, phenylpropanolamine, pseudoephedrine, promethazine or triprolidine. Due to the diversity of these substances the selectivity of the test procedures described below may not be sufficient for all products under investigations. If the chromatogram obtained provides evidence that other active ingredients or excipients interfere with the levomethorphan determination the analyst shall modify the analytical procedure, e.g. by adding further extraction steps.

Also depending on the additional active ingredients or the excipients in the product to be examined it may be necessary to flush the column with a mobile phase consisting of 950 volumes of 2-propanol R, 50 volumes of n-hexane R and 1 volume of diethylamine R after each run.

### Limit test for levomethorphan in dextromethorphan containing oral solutions

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 cellulose tris(4-methylbenzoate) groups (5 µm).<sup>1</sup> As the mobile phase use a mixture of 940 volumes of n-hexane R, 60 volumes of 2-propanol R and 1 volume of diethylamine R.

Operate with a flow rate of 0.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 285 nm. Maintain the column at 30°C.

Prepare the following solutions. For solution (1) transfer a quantity of the oral solution containing the equivalent of 50 mg of Dextromethorphan hydrobromide to a separation

<sup>1</sup> A Chiralcel OJ-H column was found suitable.

funnel. Add sodium hydroxide (~40 g/L) TS until the solution has a pH value greater than 11 (check the value using pH-indicator paper). Extract the solution with three 50 mL volumes of hexane R. Dry the combined extracts over 3 g anhydrous sodium sulphate R, filter, wash the residue with 30 mL of hexane R, combine the hexane extracts in a round-bottom flask and evaporate to dryness. Add 2.0 mL of 2-propanol R to dissolve the residue and transfer the solution to a 10.0 mL flask, wash the round-bottom flask with further 2.0 mL of 2-propanol R and also transfer the solution to the 10.0 mL flask. Dilute to volume with mobile phase. For solution (2) dilute 5.0 mL of solution (1) to 100.0 mL with mobile phase. Dilute 2.0 mL of this solution to 100.0 mL with mobile phase. Prepare solution (3) as indicated in the leaflet of Dextromethorphan for system suitability RS (containing a mixture of dextromethorphan and levomethorphan).

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the two principal peaks due to levomethorphan (retention time about 9 minutes) and due to dextromethorphan (retention time of about 12 minutes) is at least 3.

Inject alternately 20 µL each of solutions (1) and (2).

In the chromatogram obtained with solution (1) the area of any peak corresponding to levomethorphan is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

#### **Limit test for levomethorphan in dextromethorphan containing capsules and lozenges**

Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the chromatographic conditions given under Limit test for levomethorphan in dextromethorphan oral solutions.

For solution (1) transfer a quantity of the contents of the capsules (hard gelatin capsules)/ transfer a number of capsules (soft gelatin capsules) or lozenges, containing the equivalent of about 50 mg of Dextromethorphan hydrobromide to a 100 mL conical flask, add about 50 mL of water and heat and shake on a steam bath for about 15 minutes. Allow to cool, filter and transfer the eluate to a separation funnel. Wash the flask and the filtrate with 2 times 10 mL of water. Combine the aqueous solutions and add sodium hydroxide (~40 g/L) TS until the solution has a pH value greater than 11 (check the value using pH-indicator paper). Extract with three 50 mL volumes of hexane R. Dry the combined extracts over 3 g anhydrous sodium sulphate R, filter, wash the residue with 30 mL of hexane R, combine the hexane extracts in a round-bottom flask and evaporate to dryness. Add 2.0 mL of 2-propanol R to dissolve the residue and transfer the solution to a 10.0 mL flask, wash the round-bottom flask with further 2.0 mL of 2-propanol and also transfer the solution to the 10.0 mL flask. Dilute to volume with mobile phase. For solution (2) dilute 5.0 mL of solution (1) to 100.0 mL with mobile phase. Dilute 2.0 mL of this solution to 100.0 mL with mobile phase. Prepare solution (3) as indicated in the leaflet of Dextromethorphan for system suitability RS (containing a mixture of dextromethorphan and levomethorphan).

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the two principal peaks due to levomethorphan (retention time about 9 minutes) and due to dextromethorphan (retention time of about 12 minutes) is at least 3.

Inject alternately 20 µL each of solutions (1) and (2).

In the chromatogram obtained with solution (1) the area of any peak corresponding to levomethorphan is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

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