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The 18th ICDRA will be hosted by the Health Products Regulatory Authority (HPRA) of Ireland and the World Health Organization
Dublin, Ireland, 3–7 September 2018
http://www.icdra2018.ie/

Abbreviations and websites

CHMP Committee for Medicinal Products for Human Use (EMA)
EMA European Medicines Agency (www.ema.europa.eu)
EU European Union
FDA U.S. Food and Drug Administration (www.fda.gov)
HPRA Health Products Regulatory Authority, Ireland (www.hpra.ie)
ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (www.ich.org)
IGDRP International Generic Drug Regulators Programme (https://www.igdrp.com)
MHLW Ministry of Health, Labour and Welfare, Japan
MHRA Medicines and Healthcare Products Regulatory Agency, United Kingdom (www.mhra.gov.uk)
Medsafe New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz)
Ph. Int The International Pharmacopoeia (http://apps.who.int/phint/)
PIC/S Pharmaceutical Inspection Co-operation Scheme
PRAC Pharmacovigilance Risk Assessment Committee (EMA)
PMDA Pharmaceuticals and Medical Devices Agency, Japan (www.pmda.go.jp/english/index.htm)
Swissmedic Swiss Agency for Therapeutic Products (www.swissmedic.ch)
TGA Therapeutic Goods Administration, Australia (www.tga.gov.au)
U.S. United States of America
WHO World Health Organization (www.who.int)

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

Product information supplied with selected antiretrovirals in five African countries

WHO-prequalified antiretrovirals (ARVs) are widely used in HIV treatment programmes of Member States. For each prequalified medicine, a detailed WHO Public Assessment Reports (WHOPAR) is available on the WHO Prequalification website.

As part of a WHO quality monitoring study, the documents supplied with 107 samples of selected ARVs in five African countries were compared with the product information shown in the WHOPAR (for prequalified products) or publicly available information for the innovator product (for non-prequalified products). Deviations, some of them potentially impacting on patient safety, were found for most of the samples. It is recommended that regulators, procurers, health professionals and patients make more use of the WHOPARs to verify that the product information supplied with prequalified medicines conforms to that accepted by WHO.

Background
The product information accompanying a medicine is crucial to ensure its appropriate use. The aim of this study was to assess the content and readability of the product information accompanying selected ARV products in five African countries.

The study was conducted in the context of a quality monitoring survey of selected ARVs funded in large volumes by the Global Fund to Fight AIDS, Tuberculosis and Malaria.(1) The survey focused on paediatric formulations, medicines with five or more prequalified generics on the market, and products of which substandard or falsified versions had been reported to the WHO Global Surveillance System.

WHO prequalification is widely relied upon in procurement by UN-funded programmes and other international donors. For each prequalified medicine a detailed WHO Public Assessment Reports (WHOPAR) is published on the website of the Prequalification Team–Medicines (PQTm), including the approved product information for health professionals.

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2 External expert to WHO Prequalification Team
3 Technical Officer, WHO Technical Assistance and Laboratory Services
4 Contractor, WHO Essential Medicines and Health Products

RK coordinated the quality monitoring survey; RL contributed to the survey protocol. SB analyzed the product information. SB, RL and RK drafted the research report. MZ wrote the manuscript. We thank Dr Jitka Sabartova for her contributions to the main sample testing survey and for helpful comments on the manuscript.
and for patients (see Box 1). The WHOPARs are an extremely valuable resource for regulators and procurement organizations to verify the content of product information for prequalified medicines. They can also be used by health care professionals and patients looking for information about the medicines that they dispense and use.

**Methodology**

Samples of the ARVs selected for the survey were collected from September to November 2015 at 49 sites (national medicines stores, major dispensing facilities and treatment centres) in Burkina Faso, Rwanda, Nigeria, the Democratic Republic of the Congo and Zambia and sent to prequalified quality control laboratories for testing. At the laboratories the product information was extracted and forwarded to WHO for review.

The medical content and structure of the product information supplied with prequalified products was compared with that shown in the WHOPAR. For non-prequalified products it was compared with the product information of the

<table>
<thead>
<tr>
<th>tablets (innovator product: Combivir*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC/ZDV 30/60mg dispersible tablets (six samples of conventional tablets were also collected)</td>
</tr>
<tr>
<td>3TC/NVP/ZDV 30/50/60mg dispersible tablets (one sample of adult strength was also collected)</td>
</tr>
</tbody>
</table>

---

Box 2: Product information available on the WHO Prequalification website
https://extranet.who.int/prequal/key-resources/prequalification-reports/whopars

Overview of WHO Public Assessment Report (WHOPAR)
HA### - Nevirapine - 50mg - Dispersible tablets - [Manufacturer name]

Part 1 – Abstract
Part 2a – All accepted presentations
Part 2b – Visual appearance of the product
Part 3 – Patient Information Leaflet
Part 4 – Summary of Product Characteristics
Part 5 – Label
Part 6 – Discussion (status at the time of prequalification)
Part 7 – Steps before Prequalification
Part 8 – Steps following Prequalification

<table>
<thead>
<tr>
<th>Part 3: PIL</th>
<th>Part 4: SmPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine 50mg Dispersible Tablets</td>
<td>Nevirapine 50mg Dispersible Tablets</td>
</tr>
<tr>
<td>[Company name], HA### July 2016</td>
<td>[Company name], HA### July 2016</td>
</tr>
</tbody>
</table>

PATIENT INFORMATION LEAFLET

[Product name]
Nevirapine 50mg Dispersible Tablets

Read all of this leaflet carefully before you start giving this medicine to your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your healthcare provider.
- This medicine has been prescribed for your child. Do not pass it on to others. It may harm them, even if their signs of illness are the same as those of your child.
- If your child gets any side effects, talk to your healthcare provider. This includes any possible side effects not listed in this leaflet. See section 4.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
[Product name]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each dispersible tablet contains 50 mg of nevirapine (as anhydrous). Excipients with known effect: each tablet contains 41 mg of lactose monohydrate and 4.25mg of aspartame (see section 4.4) For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Dispersible tablet
White to off-white coloured, circular shaped, biconvex uncoated
innovator product established on the WHO comparator list,\(^2\) if any (see footnote 1). The innovator product information was accessed from the EMA website.\(^2\)

As in a previous study \(^3\) the following elements were compared: indications, dosing, contraindications, warnings, interactions, side effects, and pharmacological parameters (including mechanism of action, clinical efficacy, resistance, absorption and bioavailability, distribution, metabolism, elimination, pharmacokinetics in special populations and preclinical data).

The readability and usefulness of the patient information leaflets was assessed using adapted versions of the following tools:

- The Baker Able Leaflet Design (BALD) score \(^4\) for good design characteristics in terms of text line length, fonts, titles, pictograms and boxes, use of positive (“do…”) rather than negative (“do not…”) advice, spacing, use of colour and paper quality; a score of 20–25 of 32 possible points was considered to reflect good layout and design;\(^5\) and

- elements of the Ensuring of Quality of Information for the Patient (EQIP) score \(^6\) relating to the document’s identification data (date of revision, manufacturer details, and any statement if and how patients were involved or consulted in the production of the leaflet) and structure (use of everyday language, use of generic medicine name, personal address to the reader, respectful tone, clear and balanced information, logical sequence, quality of graphs, figures and layout). Each applicable item was scored as being fully met (1 point), partly met (0.5 points) or not met (0 points), and the total was expressed as a percentage of possible points.

In addition, the sampling teams interviewed the staff at the sampling sites and asked them to complete two questionnaires. One served to explore the respondents’ perceptions of the completeness and usefulness of the product information supplied with ARVs, and sources of additional information. The other focused on the acceptability of dispersible ARVs.

### Results

#### Sample

A total of 126 ARV samples were included in the survey. The samples originated from eight different manufacturers, all based in India. They represented:

- 21 prequalified products (98 samples);
- 6 products listed on the prequalification list based on U.S. FDA tentative approval (23 samples); and
- 2 products under WHO assessment at the time of the product information analysis (5 samples).

Product information for 121 samples was forwarded to WHO for analysis. In 14 cases this was for tentatively FDA-approved products that had no publicly available labelling information, and no corresponding innovator product was established on the WHO comparator list. The product information of 107 samples was therefore reviewed. For one prequalified product (five samples) the product information was mistakenly compared with that of the innovator product instead of the WHOPAR.

#### Quality of product information

### Structure

Of the 107 sets of product information accompanying the samples

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Product information supplied with selected ARVs in five African countries

- 51 had a WHOPAR-like structure, 14 of them included a PIL;
- 30 had a document titled “Prescribing information” with a PIL-like structure and some essential information for prescribers missing, none included a PIL;
- 17 had product information resembling the “Highlights of prescribing information” and “Patient counseling information” sections known from U.S. FDA-approved products, 4 included a PIL; and
- 9 had product information that did not fall into any of the above categories and was repetitive and/or very detailed, all included a PIL.

**Readability and user-friendliness**
The format and layout of the product information did not meet the criteria for easy readability: 24 of 107 documents reviewed were in font sizes much smaller than 8 points and could only be read with a magnifying glass. Some had very faint printing, which hampered reading additionally. The paper size of all except the PIL-like “Prescribing information” documents was too large (up to A2 format). A PIL was included in 28 of the documents, although none had a perforation line allowing to detach it. The BALD scores for the 28 PILs ranged from 7–15 out of 32, with a mean score of 9.8 and a median of 10. Thus none of the PILs met the BALD score considered acceptable in this study.

The EQIP criteria used in the study were only partly met. In all 28 PILs the generic name of the medicine was used. Most addressed the patient personally and presented information in a logical order. On the other hand, only 12 were written in easily understandable everyday language, only 13 had a revision date, and only 6 of these had been revised in the last seven years. Few presented balanced information on risks and benefits of medicines (see below). The mean EQIP score was 59.8% and the median score was 57%; only four PILs scored more than 64%.

**Medical content**
Of 107 SmPCs reviewed, 4 were fully in line with the information in the WHOPAR or the product information for the innovator product, 15 had minor deviations (for example because they included a different set of pharmacological parameters), and 88 had one or more substantial deviations.

Of the 107 samples, only 28 were accompanied by a PIL. Similarly as for the SmPCs, deviations from the WHOPAR or innovator product information were common in the PILs reviewed.

The numbers of deviations found in the different sections of the SmPCs and PILs are summarized in Figures 1 and 2.

**Questionnaires**

**Sources and use of product information**
In total, 51 questionnaires were completed by the sampling site staff – mainly pharmacists and clinicians – during interviews, and evaluated. Not all respondents answered all the questions. Additional statements were recorded in interviews conducted by the sampling teams.

**Type of product information received:**
The types of product information said to accompany most ARVs at the sampling sites differed from those observed in the study: 21 of 44 respondents said that they received a PIL alone (by this some may have meant the PIL-like “Prescribing information” seen in the study), 15 said both a PIL and an SmPC, and only 6 said that they received an SmPC alone.

**Information for health professionals:**
The most commonly used information
Medical content of product information: numbers of deviations found

**Figure 1:** Numbers of deviations found in summaries of product characteristics (SmPC)

<table>
<thead>
<tr>
<th>(n = 107)</th>
<th>In line with public information</th>
<th>Deviations</th>
<th>Major deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage *</td>
<td>19</td>
<td>2</td>
<td>86</td>
</tr>
<tr>
<td>Indication **</td>
<td>43</td>
<td>6</td>
<td>58</td>
</tr>
<tr>
<td>Interactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacol. parameters</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warnings</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td>41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Some samples had more than one type of major deviation

**Dosage, major deviations:**
- Missing additional dosage information (77 samples)
- Missing weight band (27 samples)
- Dosing for children included in products for adults (25 samples)
- Wrongly assigned weight band (9 samples)
- Wrong number of tablets (2 samples)

**Indications, major deviations:**
- Inclusion of children in products for adults (30 samples),
- Missing weight restriction (18 samples)
- Exclusion of children (7 samples)
- Wrongly assigned weight restriction (4 samples)

**Figure 2:** Numbers of deviations found in patient information leaflets (PIL)

<table>
<thead>
<tr>
<th>(n = 28)</th>
<th>In line with public information</th>
<th>Deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Precautions</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Contraindication</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td>19</td>
</tr>
</tbody>
</table>

No PIL – 79 samples

Sources were WHO or national treatment guidelines (44 respondents), the product information in the pack (30), the internet (13), and hospital formularies (7). Nineteen (19) respondents found the SmPCs in the product packs complete and sufficient for their needs, while 18 answered that they needed additional information. All except 2 respondents stated that they rarely or never accessed the WHO Prequalification website; one did not answer the question. WHOPARs were known to 15 respondents, 9 of whom stated that they had never used them.

**Information for patients:** The impact of the PIL on appropriate dosing and treatment compliance was rated as “crucial” by 25 respondents and as “minimal” by 22. While 20 respondents thought that the PIL provided sufficient information for patients, 25 did not think so; 17 felt that the PIL is of little use because it is not written in local language, and 3 mentioned that it is not
useful for illiterate patients. Dispensers in Burkina Faso said that some patients take only the tablets with them, leaving the product pack and the PIL behind at the facility to avoid stigmatization in the community.

Six respondents found the PILs difficult to read, 8 found the print too small, and 8 thought there was too much information. This is consistent with the low BALD scores found in the study.

**Acceptability of dispersible ARV tablets for use in children**

A total of 47 questionnaires were evaluated. Not all the respondents answered all the questions.

On the whole, the most frequently used dispersible ARV products as identified by the respondents were consistent with those sampled in the survey. Most respondents stated that they never or rarely received complaints about the taste, flavour or other aspects of dispersible ARVs.

While all except 4 respondents said that the instructions for dispersible products are easy to understand, their choices among four predefined definitions of “a small amount of liquid” in which to disperse the tablets varied widely: Less than 5 ml (5 respondents), 5–10 ml (19), 10–50 ml (5), and 50–100 ml (13). According to the WHOPARs, each tablet should be dispersed in 10 ml water.

**Discussion**

Despite the small sample size and some other limitations, this survey led to a better understanding of the quality, readability, format and use of the product information provided with ARV medicines in the African countries surveyed in this study. The results point to substantial shortcomings in terms of content and format.

Deviations from the medical information shown in WHOPARs or innovator product information were common. Some posed a direct risk for patient health. Thus, 30 of 107 SmPCs reviewed included a therapeutic indication and a dosage for children, although the prequalified or innovator product was recommended for use in adults only. This is concerning, as appropriate dosing for children cannot always be achieved with a dosage form and strength designed for adults. Two SmPCs of a paediatric ARV specified a higher dose for a specific weight band than that given in the WHOPAR, which could lead to potentially serious adverse effects. Information on dose adjustments and interactions – for example with contraceptives, antimalarials and herbal preparations – was missing in several cases, with a potential negative impact on treatment success and/or adherence. Less serious deviations pertained for example to missing therapeutic indications for adolescents and children. While this does not directly impact patient safety, it may restrict the treatment options for these patient groups.

Only 26% of the samples reviewed included a PIL, and the highest BALD score seen (15 points) was far below the score considered to represent good layout and design characteristics.

Less than 50% of the samples tested in the survey were registered in the country of use; the others were placed on the market through special permission mechanisms e.g. for donations or central supply to government centres. None of the NRAs of the surveyed countries was able to provide copies of the approved product information. In this study, different versions of the product information for the same medicine were seen in the same country. It therefore appears unlikely that the deviations
observed in the study were a result of national regulatory requirements.

The WHO survey team has communicated the findings to the regulators of participating countries and the manufacturers whose products were sampled in the study. The importance of complete and correct product information, and the possibility to verify this against publicly available WHOPARs, will be emphasized by WHO Prequalification Team in future interactions with stakeholders.

Conclusions and recommendations

Procurers and resource-constrained regulators rely on stringent assessment mechanisms, including WHO prequalification, to ensure that ARVs meet internationally accepted standards. This study found that the product information supplied with the sampled ARVs did not meet these standards.

Approving the product information supplied with medicinal products is a regulatory responsibility. However, buyers of medicines, health professionals and patients all have a role to play in making sure that the documentation supplied with products is complete and correct. Rapid action should be taken to increase the awareness and use of WHOPAR information by regulators, procurers, health professionals and patients. The development of a Prequalification App for mobile phones may be considered. Such a PQ-App would allow the easy selection of all WHOPARs available, with key features like dosing, therapeutic indications and contraindications displayed directly on the mobile phone.

In addition, manufacturers and regulators should be sensitized to the requirements for leaflet design and formatting to ensure that the product information is understood by health professionals and patients.

References

Safety of medicines

Pharmacovigilance Programme of India

The journey travelled and the way forward

Pharmacovigilance is important in assuring the safety of medicines and protecting patients from harm. The Pharmacovigilance Programme of India (PvPI) is a robust scientific platform that provides valuable information on the safety of medicinal products and contributes to regulatory decisions. Recent changes in the regulation of the drug approval processes and pre- and post-approval vigilance of undesired effects have strengthened pharmacovigilance in India. This article gives an overview of pharmacovigilance structures and practices, their integration into public health programmes, the regulatory context, recent initiatives undertaken by PvPI, challenges to overcome, and the way forward.

Introduction

All medicines carry some risk of harm. It is therefore important to monitor their effects, both intended and unwanted, to get an evidence-based assessment of risk versus benefit. Today it is well recognized that a reliable pharmacovigilance system is essential for rational, safe and cost-effective use of medicines and therefore has clear advantages in relation to cost for public health. (1)

Pharmacovigilance in India has huge socio-economic implications. The total size of the Indian pharmaceutical industry was about US$ 33 billion in 2016, making it the world’s third largest in terms of volume. (2)

An increasing part of the medicines on the Indian market are novel products. Their available baseline safety data often do not reflect the social, economic, epidemiological or health conditions of India, and their safety in everyday use still has to be proven. Establishing a standardized and robust pharmacovigilance system in India is therefore of paramount importance.

Pharmacovigilance in India

The concept of pharmacovigilance in India was first proposed in 1986 with a formal adverse drug reaction (ADR) monitoring system consisting of 12 regional centres.

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We thank Dr Clive Ondari, Coordinator, Safety & Vigilance, WHO, and Dr Lembit Rägo, Secretary General, Council for International Organizations of Medical Sciences, for their helpful inputs to this manuscript, and Mrs Monika Zweygarth for editorial services.
In 1989, six regional centres were set up under the aegis of the Drug Controller General of India. In 1997, India joined the WHO Programme for International Drug Monitoring. In 2004, the Central Drugs Standard Control Organization (CDSCO) established the National Pharmacovigilance Programme (NPVP); however in mid-2009 the World Bank funding for the NPVP ended and the programme was suspended. Recognizing the need for improved ADR monitoring in India, the Government of India proposed to work on a new framework of the programme. The Pharmacovigilance Programme for India (PvPI) was launched on a national footing in 2010 by the Ministry of Health & Family Welfare (MoHFW) of the Government of India.\(^{(3)}\)

In 2016 pharmacovigilance became a mandatory requirement under the Drugs & Cosmetics Act,\(^{(4)}\) which was amended to require all manufacturers and importers of medicines to set up pharmacovigilance systems within their company. Periodic safety update reports (PSUR) and post-marketing surveillance are described in Schedule Y of the Act. Pharmacovigilance guidelines for marketing authorization holders of pharmaceutical products were released in October 2017, together with the National Strategic Plan for Scale up of Pharmacovigilance in India, which aims to establish pharmacovigilance systems at District Hospitals, Community Health Centres (CHCs) and Primary Health centres (PHCs) under the umbrella of the national health mission, to support the existing pharmacovigilance systems in public health programmes.

### The Pharmacovigilance Programme of India (PvPI)

#### Structure
Since 2011 PvPI is coordinated by the Indian Pharmacopoeia Commission (IPC) as the National Coordination Centre (NCC) (Figure 1).

**Figure 1: Communication channels in the Pharmacovigilance Programme of India (PvPI)**

Source: Adapted from (7).
Pharmacovigilance Programme of India

ADR monitoring centres across the country collect reports from healthcare professionals and patients and submit them as individual case safety reports (ICSR) to NCC. The number of centres has increased more than tenfold from 22 in 2010 to 250 in August 2017, with many more to follow.

PvPI has a steering committee, a working group that gives technical input to CDSCO, and three expert panels to advise on technical issues. The Quality Review Panel reviews the quality and completeness of ICSRs, makes recommendations to the PvPI working group after data analysis and devises formats and guidance documents for follow-up actions. The Signal Review Panel identifies and evaluates signals from the ICSRs submitted to NCC, defines biostatistical methods for analysis and actionable indicators, and proposes appropriate regulatory interventions to CDSCO. The Core Training Panel identifies trainers, training needs and training content, and interacts with international agencies on participation and implementation of pharmacovigilance training programmes.

NCC sends the ICSRs to the WHO ICSR database, VigiBase, which is managed by the Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre for International Drug Monitoring in Sweden. UMC supports the PvPI with tools such as VigiFlow, VigiMine, VigiMed, VigiSearch, VigiLyze and VigiAccess. Currently, India's total contribution to VigiBase is more than 280,000 ICSRs. The process of ADR reporting in India has been streamlined and is supported by feedback, circulars and newsletters. Data quality has increased since 2011 and is far above the average for reporting countries globally. In 2016 the completeness score for the Indian ICSRs as per the UMC documentation grading was 0.82 out of 1.

Capacity building

Four regional resource centres provide training and technical support to AMCs of their respective regions. In addition, NCC regularly organizes national and regional programmes for training, consumer awareness and Continuing Medical Education. A Guidance document for spontaneous ADR reporting for medicines, vaccines and blood products was published in 2014. In January 2017 PvPI started a nationwide skills development programme on basic and regulatory aspects of pharmacovigilance for healthcare professionals.

Pharmacovigilance tools

PvPI, in collaboration with WHO India, has developed the PvPI toolkit, a package of simple pharmacovigilance tools in line with WHO guidelines and current best practice. The toolkit includes an ADR reporting form, which is available in Hindi and nine other regional languages to encourage direct patient reporting. There is also a feedback form for stakeholders.

To extend the outreach of PvPI to remote areas a toll-free helpline (1800 180 3024) with SMS feedback facility has been launched. The helpline is manned during working hours, missed calls are followed up the next day. The ADR reporter information is communicated to the nearby monitoring centres to allow any follow-up.

An android mobile application for reporting ADRs was launched in May 2015 by PvPI in collaboration with NSCB Medical College, Jabalpur. The application has built-in functionality for customization.

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1 JSS Medical College, Mysore (south), Seth GS Medical College & KEM Hospital, Mumbai (west), Post Graduate Institute of Medical Education and Research, Chandigarh (north), and Institute of Post Graduate Medical Education and Research, Kolkata (east)
of reporter details, auto-entry of drug details and WHO algorithm-based causality assessment. In October 2017, NCC developed an advanced version of the application with features that support source document and image attachment, XML generation and auto-filling of report details. PvPI also uses social media including LinkedIn (NCC PvPI), WhatsApp (7042343309), Facebook (Ncc-PvPI Ipc) and Twitter (@IPCNCCPvPI).

Catalysts
Three recent initiatives have acted as catalysts for vigilance strengthening in India:

Firstly, at the end of a comprehensive review conducted from 13-17 February 2017, WHO experts concluded that the national regulatory authority (NRA) and affiliated institutions in India continue to meet the requirements for a functional vaccine regulatory system as defined in the WHO global benchmarking tool (GBT). Pharmacovigilance is one of the core functions in the GBT and was assessed at Maturity Level 4 – the highest level – during the benchmarking exercise in India.

Secondly, in 2017 the NCC became a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services. This is the first WHO Collaborating Centre on this theme. Its tasks are to develop tools and guidelines for enhancing pharmacovigilance practice in low- and middle-income countries (LMIC), to contribute to capacity building in WHO Member States, and to provide scientific support to countries for pharmacovigilance in public health programmes and regulation.

Thirdly, India is actively engaged in the South East Asia Regulatory Network (SEARN) in a move to increase access to high quality medical products in WHO Member States. Vigilance of medical products is one of the four core priority areas of SEARN.

Collaboration with public health programmes
Optimizing the safety of medicines used in public health programme is essential to maximize the benefits of these programmes and maintain public confidence. The WHO Country Office for India has been engaged in providing pivotal strategic and technical support to the PvPI in setting up pharmacovigilance systems in the national immunization programme and in treatment programmes for tuberculosis, HIV/AIDS and vector-borne diseases.

Universal Immunization Programme (UIP)
An adverse event following immunization (AEFI) is “any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of vaccine”.(6) Adverse reactions to vaccines are rare but may become apparent when a large cohort is vaccinated. It is important to report and investigate each AEFI in order to determine whether it is causally linked to a vaccine and to take appropriate action.

The AEFI surveillance system in India was initiated in 1988. Reports on AEFIs are collected by monitoring centres throughout the country. AEFI committees have been constituted at state and district levels to regularly review and analyze AEFI reports. The support of the WHO National Polio Surveillance Project network is being leveraged at state and district levels.

At the national level the system is handled by three partner entities, namely CDSCO, MoHFW, and NCC. The Pharmacovigilance Division (Human vaccine) of CDSCO’s
Biological Division monitors all post-licensure activities of vaccines for regulatory decision-making. The AEFI Secretariat at the MoHFW’s Immunization Technical Support Unit (ITSU) collects and collates AEFI data for the National AEFI Committee to review. The NCC’s Signal Review Panel analyzes AEFI reports and forwards its observations to the National AEFI Committee, to recommend regulatory actions to CDSCO.

The achievements of the AEFI division at the MoHFW, with WHO support, have strengthened pharmacovigilance of vaccines in India. Communication Guidelines for Building Vaccine Confidence around AEFI were released in 2013, and training has been undertaken in 8 states. Quality management system, AEFI surveillance and response operational guidelines, standard operating procedures, training and a pilot online reporting project have also been established. As a result, AEFI reporting has increased from 398 in 2012 to 1393 in 2016. However, considering the large number of vaccine doses given to children in India there is scope for further improvement.

WHO has also provided technical, operational and financial support to the follow up of a landmark study on the potential association of all-cause death and hospitalization with routine UIP vaccinations administered to a cohort of infants in Kerala and Tamil Nadu states of India, in line with the government’s commitment to scale up the pentavalent vaccine in India. The study has provided some interesting learnings for countries in the region on pentavalent vaccine and routine UIP vaccines.

**HIV and tuberculosis programmes**

Treatment for HIV and tuberculosis often involves a significant pill burden. A patient diagnosed with tuberculosis may take 4–14 medicines concurrently, with regimens lasting from six months to two years or more, increasing the likelihood of ADRs. Adverse events can cause patients to interrupt their treatment prematurely, which can contribute to avoidable morbidity, drug resistance, treatment failure, reduced quality of life, or death. It is important that ADRs, especially serious ones, be routinely monitored. WHO has produced handbooks on pharmacovigilance for anti-tuberculosis and antiretroviral medicines.

A memorandum of understanding (MOU) was signed between IPC as the NCC for pharmacovigilance and the National AIDS Control Organization (NACO) in September 2014 for setting up systems and processes for reporting, analysis and monitoring of ADRs due to antiretroviral medicines. In a first phase, 37 ART centres were identified among the existing PvPI monitoring centres, and focal personnel were trained.

A similar MOU was facilitated between IPC and the Revised National Tuberculosis Programme (RNTCP), one of the largest public health programmes in India. In December 2014 WHO, IPC, RNTCP and NACO, in collaboration with PvPI, organized a joint workshop on ADR monitoring, reporting and causality assessment for medical and statistical officers from treatment centres all over India.

A focus is on monitoring of bedaquiline, which was launched in March 2016 for the treatment of multidrug-resistant tuberculosis under RNTCP’s Conditional Access Programme (CAP), together with guidelines on the Prevention and management of ADRs associated with antitubercular drugs. Currently there are 19 sites where at least one patient has been initiated on bedaquiline, and training has been conducted to expand
the programme to additional sites across India. WHO is supporting PvPI in setting up systems for reporting of adverse events in patients treated with bedaquiline. A prospective, observational Cohort Event Monitoring (CEM) of adverse events with bedaquiline is being implemented as part of CAP. Data are recorded upon treatment initiation and at every follow-up visit or whenever an event is reported. The data from CEM are entered into Nikshay, the electronic database used by the tuberculosis programme in India, from where they are automatically transmitted through a bridge application to the VigiFlow database used by PvPI to record ICSRs. A Drug Safety Monitoring Committee will review the use of bedaquiline and provide recommendations on its scale-up in India based on the analysis of the data from CEM.

**Vector-borne diseases programme**

PvPI (with WHO support) is collaborating with the National Vector Borne Disease Control Programme (NVBDCP) to set up focused pharmacovigilance systems for medicines used in vector-borne diseases. An MOU was signed in August 2016. In February 2017 WHO, in collaboration with NVBDCP and PvPI, organized a national meeting to accelerate Kala-azar elimination, in conjunction with a national pharmacovigilance workshop. This was followed by five regional workshops which reached a total of 530 participants in all endemic districts of four Indian states. Reporting of ADRs to Kala-azar medicines started in April 2017.

**Deworming programme**

Once a year, on national deworming day, all enrolled and out-of-school children aged 1 to 19 in schools and child care centres are given albendazole deworming tablets. This is followed by a “mop-up day” to deworm children who could not be treated on national deworming day. Two ADR reporting forms – one for healthcare professionals and one for consumers – have been included in the protocol and made available as annexure to the National Guidelines for Deworming Day.

**Collaboration with medical organizations**

IPC has identified six institutions affiliated to the Indian Council for Medical Research (ICMR) for focused pharmacovigilance research to ensure the safety of vulnerable populations exposed to different drug regimens. This collaborative effort aims to synergize experience in pharmacovigilance and pharmacoepidemiology to bolster the country’s PvPI initiative.

The Indian Medical Association (IMA) and IPC have agreed to work together to enhance ADR reporting by clinicians. A patient safety monitoring cell equipped with skilled manpower and a dedicated helpline for ADR reporting and other logistics has been set up at the IMA headquarters in New Delhi. There will be regular training and advocacy to doctors on pharmacovigilance. IMA has also declared a “National Patient Safety Day”.

In January 2017 IPC signed an MoU with the National Accreditation Board for Hospitals and Healthcare providers (NABH) to promote monitoring and reporting of ADRs by NABH-accredited hospitals.

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2 National AIDS Research Institution (NARI), Pune; Institute of Research in Reproductive Health (IRRH), Mumbai; National Institute of Cholera & Enteric Diseases (NICED), Kolkata; National Institute of Nutrition (NIN), Hyderabad; National Institute of Epidemiology (NIE), Chennai; National Institute of Malaria Research (NIMR), New Delhi
Vigilance for medical devices
The Materiovigilance Programme of India (MvPI) was launched on 6 July 2015 to monitor adverse events occurring with the use of medical devices. IPC is collaborating with the National Health System Resource Centre (NHSRC), the Sree Chitra Tirunal Institute for Medical Sciences & Technology (SCTIMST) and CDSCO to provide technical support for regulatory actions for safe use of medical devices based on data generated in India.

Under MvPI a wide range of professionals including clinicians, biomedical engineers, clinical engineers, hospital technology managers, pharmacists, nurses and technicians can report adverse events experienced with medical devices, using the Medical Device Adverse Event (MDAE) reporting form. Medical device manufacturers, importers and traders can report adverse events specific to their products to SCTIMST. There are 10 medical device monitoring centres that accept MDAE forms for onward submission to NCC. The toll free PvPI helpline also provides assistance in reporting.

NHSRC’s Division of Health Care Technology is India’s first WHO Collaborating Centre for Priority Medical Devices & Health Technology Policy. In this role the centre frames technical specifications for medical devices, develops best practices for technology life cycle management and maintenance, assesses innovations for uptake into public health systems, and conducts health technology assessments in collaboration with WHO. Assessments of over 50 technologies have been completed and published in a compendium. NHSRC and WHO have been jointly offering Health Technology Assessment Fellowships once every six months. Over 300 professionals from across India have been trained in the past five such programmes.

Vigilance for blood products
Tracking adverse events occurring after administration of blood products is important to ensure that blood transfusions and other uses of blood products are safe and have the intended benefits in the health care system. Haemovigilance is the set of surveillance procedures covering the entire blood transfusion chain, from the donation and processing of blood and its components, through to their provision and transfusion to patients, and including their follow-up. It is intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of blood products and to prevent their occurrence and recurrence. Haemovigilance enhances patient safety by learning from failures.

The Haemovigilance Programme of India (HvPI) was launched under the umbrella of PvPI on 10 December 2012. Currently 154 centres are enrolled in this programme. The National Institute of Biologicals (NIB) is the coordinating centre for HvPI.

Challenges
Setting up a national pharmacovigilance system in India presents some formidable challenges. The health sector caters for a population of over 1.3 billion with vast ethnic variability, different disease prevalence patterns, practice of different systems of medicines and different socioeconomic status. There has been a rising disease burden with an increasing incidence of non-communicable diseases such as cardiovascular conditions and diabetes. And the country’s production and use of medical products is growing fast,
with many new and complex technologies coming to market.

One of the biggest issues, as stated by Dr Kalaiselvan, Principal Scientific Officer of PvPI in an interview with UMC, is under-reporting of ADRs. The heavy workload of healthcare professionals does not leave much time for reporting. PvPI staff at the monitoring centres – which are mostly hospitals – therefore actively solicit ADR reports from doctors and nurses. Another challenge for PvPI is that pharmacists need to be empowered to enhance ADR reporting.

Running a pharmacovigilance programme in India, with its 28 states and more than 600 districts governed by a complex public administration, is no easy task. Previous pharmacovigilance programmes in India suffered from a lack of communication and coordination. The government and policymakers in India have now recognized the importance of pharmacovigilance. This has enabled PvPI to establish the good management and working relationships needed to make it effective.

Way forward
Patient safety is a fundamental principle of health care. Delivering safer care and preventing harm, particularly “avoidable harm”, is one of the greatest challenges in today’s complex, pressurized and fast-moving environments.

As a next step, PvPI activities will be expanded to other levels of the health system in line with the national scale-up plan for pharmacovigilance in India. More district hospitals will be set up as monitoring centres. The expansion of pharmacovigilance activities will strengthen the agenda of patient safety in India, which is in line with WHO's Third Global Patient Safety Challenge: Medication without Harm.

References

2 The resurgence of pharma sector in India. Express Pharma News Bureau. 20 December 2017.
5 UMC. Documentation Grading - Completeness Score. Report for India, including data until 1 July 2014.
Safety news

Safety warnings

**Edoxaban:**  
**Interstitial lung disease**  
Japan – The PMDA has informed health professionals that cases of interstitial pneumonia have been observed in patients treated with the anti-clotting agent edoxaban (Lixiana®) in Japan. Based on the PMDA’s investigation the MHLW has recommended updates to the product information of this medicine. Patients should be carefully monitored. If signs and symptoms such as cough, shortness of breath, dyspnoea, fever or abnormal chest sound are observed, examinations including chest X-ray, chest CT scan, and serum marker test should be done immediately. If interstitial lung disease is suspected, administration of edoxaban should be discontinued and appropriate measures such as administration of corticosteroid taken.

► PMDA Summary of investigation results and MHLW Revision of precautions, 11 January 2018.

**Teriparatide:**  
**Shock and loss of consciousness**  
Japan – Following reported cases of loss of consciousness and acute hypotension in patients treated with the osteoporosis medicine teriparatide in Japan, leading to cardiac arrest and/or respiratory arrest in some cases, the PMDA has recommended that clearer warnings should be added to the product information about the risk of seizures, shock and loss of consciousness associated with the use of teriparatide. These events may occur immediately or up to several hours after administration. In some patients the onset was after several months of treatment.  

An overview of the risks of teriparatide—including hypercalcaemia, a range of side effects due to dilatation of vessels, and osteosarcoma reported in animal toxicity studies and leading to suspension of initial clinical trials—has been published in the independent drug bulletin of the Japan Institute of Pharmacovigilance. The authors conclude that the benefit/risk balance is negative in the treatment of osteoporosis.

► (1) PMDA Summary of investigation results and MHLW Revision of precautions (teriparatide acetate, teriparatide genetical recombination), 11 January 2018.  
(2) Med-Check—The Informed Prescriber (TIP). December 2017; 3(9): 34-5.

**Clarithromycin:**  
**Risk of cardiovascular events**  
United States of America – The FDA has advised caution in the use of the antibiotic clarithromycin in patients with heart disease, even for short periods. Clarithromycin is associated with a potential increased risk of heart problems or death that can occur years later. This safety issue was first observed in a large clinical trial, and was confirmed in a 10-year follow-up study in patients with coronary heart disease.

Health care professionals should weigh the benefits and risks of clarithromycin and consider prescribing other antibiotics in patients with heart disease. If such patients are given clarithromycin they should be alerted to the risks and advised to seek medical care immediately if they experience...
any signs and symptoms of a cardiovascular problems such as a heart attack or stroke. The product information has been updated.

► FDA Drug safety communication, 22 February 2018.

**Atezolizumab:**

**Myocarditis**

Canada – The marketing authorization holder, in agreement with Health Canada, has informed health professionals that severe cases of myocarditis have been reported in patients treated with the anti-cancer medicine atezolizumab (Tecentriq®) in clinical trials. Healthcare professionals should monitor patients on atezolizumab for signs and symptoms of myocarditis. Treatment should be withheld in patients with Grade 2 myocarditis, and permanently discontinued in patients with Grade 3 or 4 myocarditis. Patients on atezolizumab who develop myocarditis should receive corticosteroids and/or additional immunosuppressive agents as clinically indicated.

The Canadian product information has been updated to include this new safety information.

► Health Canada Advisory, 14 February 2018.

**Lenvatinib:**

**Gallbladder inflammation**

Japan – The PMDA has informed health professionals that cases of acute cholecystitis have been reported in patients treated with the anti-cancer medicine lenvatinib mesilate (Lenvima®) in Japan and in other countries. Two of the cases observed in Japan had a fatal outcome. A warning has been added to the product information, recommending that patient should be monitored and appropriate measures taken —such as stopping the medicine—if any abnormalities are observed.

► PMDA Summary of investigation results and MHLW Revision of precautions, 11 January 2018.

**Iomeprol, iohexol:**

**Severe skin reactions**

Japan – Following reports of acute generalized exanthematous pustulosis (AGEP) in patients treated with the iodinated contrast media iomeprol and iohexol, the PMDA has recommended updates to the product information to warn about this potential adverse effect.

► PMDA Summary of investigation results, 13 February 2018.

**Saccharomyces boulardii probiotics:**

**Do not use in critically ill or immunocompromised patients**

Estonia – The marketing authorization holder, in agreement with the regulatory authority of Estonia, has informed health professionals that *Saccharomyces boulardii*-containing probiotic products should not be used in critically ill or immunocompromised patients, as they can cause fungaemia in very rare cases. Also, special care should be taken when handling of *S. boulardii* medicinal products in the presence of patients mainly with central venous catheters, but also with peripheral catheters, in order to avoid any contamination by touch and the spread of microorganisms by air. The product information has been updated to include these warnings.

*S. boulardii* is a replacement for intestinal flora. It is used for adjuvant symptomatic treatment of diarrhoea as well as for prophylaxis and treatment of antibiotic-associated diarrhoea and recurrence of Clostridium difficile disease in addition to vancomycin and metronidazole. The update follows a review and recommendation by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC).

► Ravimiamet (Estonian medicines agency). Safety announcement, 13 February 2018. (Estonian)

(1) PRAC meeting minutes, September 2017.
**Artemisia annua soft gel capsules:**
Reports of liver damage

New Zealand – Medsafe has alerted consumers that Artemisia annua extract may pose a risk of harm to the liver. A. annua extract is marketed in New Zealand as a natural dietary supplement for maintaining and supporting joint health and mobility. The warning follows reports of liver toxicity received by the Agency’s Centre for Adverse Reactions Monitoring (CARM). All the reports involved patients taking a specific product presented as soft gel capsules. Since the chemical composition of the A. annua extract in that product was not disclosed it is not clear if other products containing A. annua extract could have similar effects.

► Medsafe Alert communication, 15 February 2018.

**Mitragyna speciosa (kratom):**
Opioid-like substance to be recalled in the U.S.

United States of America – The FDA has received numerous reports of adverse events associated with the use of food supplement products containing kratom (*Mitragyna speciosa*), including 44 reported deaths. Such products are not authorized in the U.S. The FDA has encouraged companies supplying kratom-containing products to organize a destruction and recall, and to submit data for evaluation of the products through the applicable regulatory pathway. Kratom is a plant that grows in Thailand, Malaysia, Indonesia and Papua New Guinea. The FDA has reviewed data suggesting that compounds in kratom share structural similarities with controlled opioid analgesics and have significant risks of abuse and adverse effects.

In addition the FDA and the U.S. Centers for Disease Control and Prevention (CDC) are monitoring a nationwide outbreak of a rare type of salmonella associated with kratom-containing capsules, teas and powders. This underscores the risk that unapproved products, which are not subject to manufacturing controls, may be contaminated with harmful bacteria.


**To be withdrawn from the market**

**Hydroxyethyl starch:**
Earlier restrictions not sufficient

European Union – The EMA has endorsed the recommendation by its Pharmacovigilance Risk Assessment Committee (PRAC) to suspend the marketing authorizations for hydroxyethyl-starch solutions for infusion across the EU. These solutions are used as plasma volume replacement following acute blood loss to treat hypovolaemia in case cristalloids are not sufficient to stabilize the patient.

Restrictions had been introduced in the EU in 2013 to reduce the risks of these products for critically ill patients and those with sepsis and kidney injury. The PRAC has reviewed the results of two drug utilization studies together with other available data and feedback from stakeholders and experts, and has concluded that the earlier restrictions have not been sufficiently effective.


**Daclizumab:**
Cases of inflammatory brain disorders

European Union – The EMA has recommended the immediate suspension and recall of the multiple sclerosis medicine daclizumab (*Zinbryta*®). This follows 12 cases of serious inflammatory brain disorders worldwide, including encephalitis and meningoencephalitis. Three of the
cases were fatal. The company that markets the medicine has voluntarily requested the withdrawal of the marketing authorization and has informed EMA of its decision to stop ongoing clinical studies.

No new patients should start treatment with daclizumab. Healthcare professionals should immediately contact patients on daclizumab and should stop their treatment and consider alternatives. Patients stopping treatment must be followed up for at least 6 months.(1)

In November 2017 the EMA had tightened its restrictions on the use of daclizumab introduced in July 2017 because of the risk of serious liver damage.(2) Available evidence also indicates that daclizumab could be linked to other immune-mediated disorders, such as blood dyscrasias, thyroiditis or glomerulonephritis. An urgent review is under way (see page 26).

► (1) EMA Press release, 7 March 2017.
► (2) WHO Drug Information, Issues 3 and 4 of 2017.

Flupirtine:
Serious liver problems
European Union – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the marketing authorization for the analgesic flupirtine be withdrawn. Following an earlier review, restrictions had been introduced in 2013 to limit the use of flupirtine to no more than two weeks in patients with acute pain who could not use other analgesics, subject to weekly liver function tests. These recommendations have not been sufficiently followed in clinical practice, and the PRAC could not identify any further measures that would adequately reduce the risk of liver problems associated with the use of flupirtine.


Known risks

Obeticholic acid:
Liver decompensation or failure in incorrectly dosed patients
United States of America – In an update to its communication of September 2017, the FDA has added its most prominent “Boxed Warning” and other updates to the product information for obeticholic acid (Ocaliva*) to clarify the recommendations for screening, dosing and monitoring based on the patient’s Child-Pugh score of liver impairment and any prior decompensation event. Obeticholic acid is used for the treatment of primary biliary cholangitis (PBC), a rare chronic liver disease. It has been incorrectly dosed daily instead of weekly in patients with moderate to severe PBC, increasing the risk of serious liver injury. The FDA is also requiring a medication guide for patients.

► FDA Drug safety communication, 2 February 2018.

Loperamide:
Packaging changes for safe use
United States of America – Despite earlier warnings, the FDA continues to receive reports about serious heart problems occurring with excessive doses of the antidiarrhoeal medicine loperamide. Most cases are linked to abuse or misuse of loperamide, for example to increase its euphoric effects by combining it with other drugs, or to treat symptoms of opioid withdrawal. The maximum daily dose of loperamide for adults approved in the U.S. is 8 mg per day for over-the-counter use and 16 mg per day for prescription use. The FDA is working with manufacturers to use blister packs or other single dose packaging and to limit the number of doses in a package.

Retinoid-containing medicines: Updated measures to avoid use in pregnancy, neuropsychiatric disorders

European Union – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended updated measures to avoid the use of retinoids in pregnancy as they can have harmful effects on the unborn child, and to warn about the possible risk of neuropsychiatric disorders.

The recommended pregnancy prevention measures depend on the type of retinoid. Oral medicines containing acitretin, alitretinoin or isotretinoin must be used in line with an updated pregnancy prevention programme, and the marketing authorization holders will conduct a study and a survey to assess the effectiveness of the new measures. For oral bexarotene and tretinoin, which are used under strict medical supervision to treat certain cancers, the current pregnancy prevention measures are considered appropriate. For topical retinoids the PRAC adopted a precautionary approach: Although their absorption is very low it could be increased by excessive use or skin lesions, and their use is not recommended in pregnancy or in women planning to have a baby.

A warning about the risk of neuropsychiatric disorders, such as depression, anxiety and mood changes, will be added to the prescribing information of oral retinoids. These events may be due to the medicine as well as the nature of the disease itself. No additional warning was considered necessary for topical retinoids.

Efavirenz: QT interval prolongation

Japan – The PMDA has informed health professionals about the outcomes of a clinical study, which has found that an increased blood concentration of efavirenz was associated with prolongation of the QT interval. The product information for efavirenz has been updated.

The product information approved in the EU and the U.S. states that QTc prolongation has been observed with efavirenz, and that alternatives to efavirenz should be considered in patients taking other medicine with a known risk of Torsade de Pointes, and in patients at increased risk of Torsade de Pointes.

► PMDA Summary of investigation results, 13 February 2018.

Ipilimumab: Myositis

Japan – The PMDA has recommended to include a warning about the risk of muscle inflammation (myositis) in the product information for the skin cancer medicine ipilimumab (Yervoy®) in order to align it with the product information approved in the EU and the U.S.

► PMDA Summary of investigation results, 11 January 2018.

Nintedanib: Liver injury

New Zealand, Canada – The marketing authorization holders, in agreement with Medsafe, have informed health professionals that cases of drug-induced liver injury (DILI), including one fatal case, have been reported in patients treated with nintedanib (Ofev®) in the post-marketing setting. (1, 2) Most of these events occurred in the first three months of treatment.

Nintedanib is indicated for the treatment of idiopathic pulmonary fibrosis. The product information is being updated to reflect the observed increased severity of
DILI and to provide further guidance on the monitoring schedule of hepatic laboratory testing. Similar updates have been included in the product information approved in the U.S., the EU and Japan.

 ► (2) Health Canada Advisory, 11 January 2018.

**Valproate: Updated measures to avoid use in pregnancy**

**European Union** – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended additional measures to avoid the use of valproate in pregnant women. The medicine should only be used in women of childbearing age if the conditions of a new pregnancy prevention programme are met. New visual warnings, a patient reminder card and updated educational materials will also be introduced to warn about the risk of malformations and developmental problems in infants exposed to valproate in the womb. The PRAC recognized that for some pregnant women with epilepsy it may not be possible to stop valproate, and determined that they can continue treatment with appropriate specialist care.

Valproate is used in the EU to treat epilepsy and bipolar disorder. In some EU member states it is also authorized to prevent migraine headaches. The measures taken following an earlier review have not been sufficient to mitigate the risks of valproate in pregnancy. The strengthened warnings were adopted following a second review with wide consultation, including a public hearing.


**Opioid cough and cold medicines: Labelling changes**

**United States of America** – The FDA is requiring updates to the product information for prescription cough and cold medicines containing codeine or hydrocodone to limit the use of these products to adults 18 years and older and to provide information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing. The updates are based on the outcome of an FDA review communicated in April 2017 and the recommendations of an expert panel.

► FDA Drug safety communication, 11 January 2018.

**Idarucizumab: Second dose may be needed**

**New Zealand** – Following the outcome of a full cohort study, Medsafe has alerted health professionals that some patients may need a second dose of idarucizumab (Praxbind®) to reverse the effects of dabigatran (Pradaxa®). The timing of the second dose depends on the timing of the recurrence of bleeding and the measurement of the elevated coagulation tests. More information is shown in the product’s data sheet. Idarucizumab is indicated in patients treated with dabigatran when rapid reversal of dabigatran’s anticoagulant effect is required for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding.


**Gadolinium-based contrast agents**

**United States of America** – Based on results of an additional review the FDA is requiring a new class warning for gadolinium-based contrast agents, alerting health professionals and patients to the risks caused by long-term gadolinium retention in the body. A
patient medication guide will be introduced, and manufacturers have been requested to conduct further human and animal safety studies. (1)

In the EU a final decision on restrictions for linear gadolinium-based contrast agents has been published following the conclusion of the EMA’s regulatory review in July 2017. The restrictions recommended earlier were maintained. (2)

(1) FDA Drug safety communication, 19 December 2017.

(2) EMA’s final opinion confirms restrictions on use of linear gadolinium agents in body scans, 23 November 2017.

Interim recommendations

Ulipristal:
No new treatment courses to be started
European Union – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that, pending the outcome of its ongoing review of ulipristal (Esmya*), no patients should start new or repeat treatment courses with ulipristal for uterine fibroids. In women currently on treatment, liver function should be monitored at least once a month. If liver enzyme levels are more than twice the upper limit of normal, treatment should be stopped and the patient closely monitored, and the liver function tests should be repeated 2–4 weeks after stopping treatment.

Ulipristal is under EMA review following reports of serious liver injury, including liver failure leading to transplantation.


Recombinant live-attenuated dengue vaccine
WHO has published its interim position on the use of the recombinant, live-attenuated dengue vaccine Dengvaxia*. (1) Vaccination is recommended only in individuals with a past dengue infection, as documented either by a diagnostic test or by a documented medical history of past dengue illness. This follows a review of preliminary results provided by the manufacturer. Further WHO guidance on the matter is expected no earlier than April 2018.

In 2016 the WHO Strategic Advisory Group of Experts on Immunization (SAGE) had recommended the vaccine for use in endemic areas with a seroprevalence over 70%. (2) A theoretical elevated risk of dengue in vaccinated seronegative individuals was noted, prompting additional research by the manufacturer. Preliminary findings suggest that the subset of trial participants who had not been exposed to dengue virus prior to vaccination had a higher risk of more severe dengue and hospitalizations than unvaccinated participants. This increased risk was seen after an initial protective period and persisted over the observation period of up to 66 months after primary vaccination.

Dengvaxia* has been introduced in subnational programmes in the Philippines and Brazil targeting about one million individuals in total. It is otherwise available on the private market in countries where there is a marketing authorization. The manufacturer has proposed a labelling change to the national regulatory authorities in the countries where Dengvaxia* is licensed.

(1) WHO. Updated Questions and Answers related to the dengue vaccine Dengvaxia® and its use. 22 December 2017.


Radium-223 dichloride:
Must not be used with abiraterone and prednisone / prednisolone
European Union – The EMA has recommended contraindicating the
use of the prostate cancer medicine radium-223 dichloride (Xofigo®) with abiraterone (Zytiga®) and prednisone / prednisolone due to an increased risk of death and fractures. Healthcare professionals should stop this combination in men currently treated with it and review the treatment for these patients. The safety and efficacy of radium-223 in combination with second-generation androgen receptor antagonists, such as enzalutamide (Xtandi®), have not been established.

The contraindication was introduced by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) as a temporary measure in view of the seriousness of the events reported in a clinical trial. An in-depth review of the benefits and risks of radium-223 is ongoing.


**Warnings softened**

**Direct-acting antivirals:**
**Effect on blood glucose not confirmed**
New Zealand – Medsafe has provided an update on its monitoring communication issued in March 2017, which highlighted a possible blood glucose-lowering effect of the direct acting antivirals Viekira Pak® and Viekira Pak-RBV® when used in patients with type 2 diabetes. No further cases were reported in New Zealand, and the effect could not be confirmed.

► Medsafe monitoring communication, 31 January 2018.

**Mycophenolate:**
**Updated recommendations for contraception**
European Union – The EMA has updated its recommendations for contraception in men and women taking mycophenolate-containing medicines to prevent rejection of transplanted organs. The previous recommendation that male patients should use condoms in addition to their female partners using a highly effective method of contraception has been removed. Either the male patient or his female partner should use reliable contraception during mycophenolate treatment and for at least 90 days after stopping treatment. Female patients who can become pregnant must use at least one reliable form of contraception before, during and for 6 weeks after stopping treatment. Two forms of contraception are preferred but no longer mandatory.


**Combination treatments for asthma: Warning removed**
United States of America – An FDA review of four large clinical safety trials has shown that treating asthma with long-acting beta agonists (LABAs, e.g. salmeterol, vilanterol, formoterol) in combination with inhaled corticosteroids (ICS, e.g. fluticasone, mometasone, budesonide) does not result in significantly more serious asthma-related side effects than treatment with an ICS alone. The Boxed Warning about asthma-related death has been removed from the product information of medicines that contain both an ICS and LABA.

Using LABAs alone to treat asthma without an ICS to treat lung inflammation is associated with an increased risk of asthma-related death. The warnings stating this will remain in the product information of the relevant medicines.

► FDA Drug safety communication, 20 December 2017.
**Reviews started**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Use</th>
<th>Concerns</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daclizumab</strong></td>
<td>Treatment of multiple sclerosis</td>
<td>Cases of serious inflammatory brain disorders, including 3 fatal cases.</td>
<td>► EMA Press release, 7 March 2017.</td>
</tr>
<tr>
<td><strong>(urgent review)</strong></td>
<td>(Zinbryta*)</td>
<td>Linked to potentially fatal immune-mediated liver injury in a 2017 review.</td>
<td></td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>Anti-thrombotic agent</td>
<td>Possible risk of gout or gout-like symptoms (one case report in New Zealand, and reports in WHO's VigiBase)</td>
<td>► Medsafe Monitoring Communication, 31 January 2018.</td>
</tr>
</tbody>
</table>

**Compliance with good practices**

**Svizera Labs Pvt Ltd:**
**Notice of Concern withdrawn**
Following corrective actions taken by Swizera Labs Pvt Ltd and the clarifications provided being considered acceptable, and considering the outcome of an additional on-site inspection on 25–29 June 2017, the WHO Prequalification Team - Medicines has withdrawn the Notice of Concern (NOC) for Swizera Labs Pvt Ltd Mumbai, India. The NOC had been issued on 2 September 2015 after an inspection of the company’s site at Turbhe, Navi Mumbai, India.

**Qinhuangdao Zizhu Pharmaceutical Co Ltd:**
**Corrective action under way**
Geneva – The WHO Prequalification Team–Medicines has provided an update on the level of compliance with good manufacturing practices (GMP) by Qinhuangdao Zizhu Pharmaceutical Co Ltd. On 8 March 2017 the U.S. FDA had placed an import alert on the company, following observations of serious breaches of data integrity and other GMP failures during an inspection of the company’s site located at No. 10, Longhai Avenue, in Qinhuangdao, Hebei Province, China.

A WHO inspection of the site in December 2017 revealed that the company had only partly addressed the FDA’s observations. A follow-up WHO inspection is planned for October 2018 to verify that the company has implemented its corrective and preventive action (CAPA) plan as submitted to WHO.

Qinhuangdao Zizhu manufactures three prequalified active pharmaceutical ingredients (APIs) – levonorgestrel, mifepristone and ethinylestradiol – and supplies levonorgestrel for two prequalified finished products. To date WHO has not received any complaints relating to the quality of prequalified levonorgestrel tablets. WHO is working closely with the manufacturers of prequalified levonorgestrel tablets to identify alternative API sources, and has requested them to take additional measures to ensure that all API batches from Qinhuangdao Zizhu meet their specifications.
Falsified medicines

Falsified cefixime products circulating in the Democratic Republic of the Congo

The WHO Medical Product Alert No. 1/2018 relates to two versions of falsified cefixime products that have been identified in the eastern part of the Democratic Republic of the Congo (South Kivu) and were reported to WHO in late 2017. Cefixime is used to treat a range of bacterial infections and is listed as a WHO Essential Medicine.

The products were sent for quality assurance laboratory testing and the results shared with WHO (see table). Both products are presented in standard white plastic containers of 100 tablets. The tablets of both products are round, small, and without any embossing. The labels of both products have spelling mistakes. Product details are shown below.

<table>
<thead>
<tr>
<th>Product</th>
<th>Cefixime Trihydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch number</td>
<td>4734</td>
</tr>
<tr>
<td>Expiry date</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>Manufacturing date</td>
<td>Nov 2014</td>
</tr>
<tr>
<td>Stated active pharmaceutical ingredient</td>
<td>Cefixime</td>
</tr>
<tr>
<td>Manufacturer name stated on the label</td>
<td>MERCK &amp; CO. INC. HOLDEN MEDICAL THE NETHERLANDS</td>
</tr>
<tr>
<td>Assay result</td>
<td>2.5% of declared content of cefixime</td>
</tr>
</tbody>
</table>

Both stated manufacturers have confirmed they did not manufacture either of these products. No adverse reactions to either product have been reported to WHO at this stage.

► WHO Medical Product Alert No. 1/2018 (includes photographs).

Falsified “Augmentin” circulating in Cameroon

The WHO Medical Product Alert No. 2/2018 relates to a falsified version of Augmentin (amoxicillin + clavulanate potassium) identified in Cameroon. WHO was informed in early 2018 by an NGO that this product was available in a street market in Douala. The packaging of the falsified product appears to be a close imitation of the genuine product manufactured by GlaxoSmithKline (GSK). The writing on the packaging has some spelling errors. GSK has confirmed that they did not manufacture this product.

Samples were sent for quality assurance testing and the results shared with WHO. The laboratory analysis did not identify any of the expected active ingredients.

The source of the falsified product has not yet been identified. No adverse reactions have been reported to WHO at this stage.

► WHO Medical Product Alert No. 2/2018 (includes photographs).

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

Pre-market assessment

Orphan medicines approvals

European Union – The EMA has started publishing its assessment reports on whether a product still fulfils the criteria for orphan designation at the time of its marketing authorization.

To qualify for orphan designation a medicine must target a disease that is life-threatening or chronically debilitating and affects less than 5 in 10 000 patients in the EU. If another treatment is available for that rare disease, the applicant must show that the new medicine offers a clinically relevant advantage or a major contribution to patients. Orphan medicines benefit from a number of incentives, including fee reductions for scientific advice during development and ten years of market exclusivity if the orphan status is maintained once the medicine is authorized.

Publication of the orphan maintenance assessment reports will increase transparency and may provide useful information for health technology assessment bodies in establishing the cost-effectiveness of a product. The reports will be published for all positive and negative opinions as well as withdrawals as part of the European Public Assessment Reports (EPARs) for medicines. Information of a commercially confidential nature will be deleted. (1)

An estimated 30 million people in the EU are affected by one of over 6 000 rare diseases. The EU’s orphan designation programme was launched in the year 2000 to incentivize research and development of medicines for these rare diseases. To date, over 1 900 medicines have been designated as orphan medicines, of which over 140 were on the market at the end of 2017. (2)

(2) EMA News, 21 December 2017.

United States of America – Metrics on requests for FDA orphan drug designations and approvals of requests and products since 1983 have been published on web. In the past 35 years the FDA has approved nearly 4 500 orphan drug designations in response to more than 6 300 orphan drug designation requests received, and has granted more than 650 marketing authorizations for orphan medicines.

FDA Law Blog post, 28 February 2018.

U.S.: Clinical data summary pilot

United States of America – The FDA has launched a pilot programme in which it will disclose parts of the clinical study reports, the summaries from the pivotal clinical trials submitted to the FDA for approval of a product. Specifically, the study report body, the protocol and amendments, and the statistical analysis plan for each pivotal study will be posted. Patient privacy and confidential commercial information in the CSRs will be protected. The pilot will include up to nine recently approved new drug applications across a range of diseases. Participation by sponsors is voluntary. The first product for which information has been posted is apalutamide, a newly approved treatment for prostate cancer.
The pilot is intended to create more transparency regarding the clinical evidence supporting marketing authorization applications and the FDA’s decision-making process. Public feedback will be sought once the pilot is complete.

Secondly, the FDA will include in the published materials relating to future approvals the identifier number from the National Institutes of Health’s clinical trial register, ClinicalTrials.gov (the NCT#). This will enable the public to link the information on clinical research on a medicine to the FDA communications published throughout the regulatory process.


U.S.: Priority reviews for medicines needed by armed forces
United States of America – Utilizing legal changes enacted in December 2017 the FDA will expedite its review of priority products to diagnose, treat, or prevent serious or life-threatening conditions that affect American military personnel, in a manner similar to products under the breakthrough designation programme.

Current high-priority products include freeze-dried plasma, cold-stored platelets, and cryopreserved platelets. The initial phase of the programme will therefore be conducted by the FDA’s Center for Biologics Evaluation and Research (CBER) and Department of Defense’s (DoD) Office of Health Affairs. As a broad and evolving range of medical products will be needed for service members, the programme will ultimately extend across the FDA’s capabilities.


### Biosimilars

#### Switzerland: Additional biological comparators allowed

Switzerland – Swissmedic will now accept reference products from additional countries for studies on comparability of biosimilars. For main studies, reference products from the U.S. are acceptable in addition to those from Switzerland and the EU. For supplementary studies, comparator products from Canada are now accepted, in addition to those from Switzerland, the EU and Japan. Furthermore, environmental risk assessments (ERA) are now compulsory for biosimilar submissions to Swissmedic.(1) The question-and-answer document on authorization of biosimilars has been updated.(2)

► Swissmedic statement, 1 January 2018.

Questions and answers concerning the authorisation of similar biological medicinal products (biosimilars). Updated 9 January 2018.

#### Australia: No suffixes for biosimilar names

Australia – Following a public consultation conducted in 2017, the active ingredient of a biosimilar will continue to be designated by the Australian biological name (ABN) without a product-specific suffix. The TGA has updated its guidance on registration of biosimilars accordingly.

Collaboration

U.S. and EU to re-focus inspection resources

The beginning of November 2017 marked a milestone in implementing the mutual recognition agreement (MRA) between the EU and the U.S. Completed assessments of each other’s inspection capabilities enabled eight regulatory authorities located in the EU and the FDA to recognize the outcomes of each other’s inspections.\(^{(1)}\)

While the EU has six existing MRAs with authorities outside the Union,\(^{(2)}\) this is a first for the FDA. The agreement will change the frequency of inspections that the participating authorities conduct in different parts of the world. In 2011–15 about 40% of the FDA’s foreign pharmaceutical manufacturing site inspections were performed in the EU. Only about 5% of these inspections gave rise to official action, compared with 14% of the FDA’s inspections conducted in India and 21% of those conducted in China.\(^{(3)}\)

Observers expect that over the next three to five years, both the FDA and the EU will shift their resources away from each other’s territories towards facilities in India and China, and are recommending that pharmaceutical manufacturing sites operating in those countries should start preparing now for that increased scrutiny.\(^{(4)}\)

\(^{(1)}\) The Mutual Reliance Initiative: A New Path for Pharmaceutical Inspections in Europe and Beyond. Posted on FDA Voice, 7 December 2017.

\(^{(2)}\) EMA. Mutual recognition agreements [webpage].

\(^{(3)}\) The Mutual Reliance Initiative: A New World for Pharmaceutical Inspections. Presentation by Dara A. Corrigan at the Food and Drug Law Institute’s Annual Conference. 5 May 2017.

\(^{(4)}\) The FDA/EU Mutual Recognition Agreement — What You Need To Know. Pharmaceutical online. Guest Column, 7 December 2017.

“3Rs”

First EMA report on actions for more ethical animal use

European Union – The EMA has published its first report summarizing the Agency’s actions to support the 3Rs principles for more ethical use of animals. “3Rs” is an acronym for replacement, reduction and refinement of animal tests. The actions described in the report are driven by the Joint CVMP/CHMP 3Rs Working Group that advises the relevant EMA committees on matters concerning the use of animals in regulatory testing of medicines.

Two new guidelines developed by the working group have been adopted, encouraging proposals for alternative testing approaches and providing guidance to individual laboratories in collaborative trials. The group also coordinates public consultations, and reviews animal tests included in lot release specifications for centrally authorized vaccines and biologicals to check compliance with current Ph.Eur monographs and to ensure that best practice in 3Rs is applied.

\(^{\uparrow}\) EMA Press release, 28 February 2018.

Under discussion

United States of America – The FDA has published draft updated guidance on issuance of public warnings and notification of recalls. The draft guidance clarifies and supplements existing policy for industry and FDA staff.
  Closing date: 20 March 2018.

United States of America – The FDA has proposed a risk-based enforcement approach to homeopathic products. The new approach addresses situations where homeopathic treatments are being marketed for serious conditions but have not been shown to offer clinical benefits, or where products labelled as homeopathic contain potentially harmful ingredients or do not meet current good manufacturing practices.(1)

The FDA continues to find that some homeopathic products are manufactured with active ingredients that can create health risks while delivering no proven medical benefits. For example, in January FDA testing found elevated amounts of belladonna in homeopathic teething products. Belladonna alkaloids can have unpredictable and potentially serious adverse effects in young children. The company did not initially agree to conduct a recall. The FDA recommended that consumers stop buying these products immediately, dispose of any in their possession, and seek medical care immediately if they observe any adverse effects in their child after use of a homeopathic teething product.(2)
► (1) FDA News Release, 18 December 2017.
  Federal Register Notice, 20 December 2017.
  Closing date: 20 March 2018.

European Union – The European Commission (EC), WHO and the Pharmaceutical Inspection Co-operation Scheme (PIC/S), have jointly proposed a revised version of the guidelines on manufacture of sterile medicinal products. The document is subject to parallel public consultation by the three entities.
  Closing date: 20 March 2018.

United States of America – The FDA has announced the availability of draft guidance for industry on Drug products, including biological products, that contain nanomaterials.
► Federal Register Notice, 18 December 2017.
  Closing date: 19 March 2018.
**Approved**

**Glibenclamide paediatric formulation for neonatal diabetes**
- **Product name:** Amglidia®
- **Dosage form:** Oral suspension
- **Class:** sulfonylurea; **ATC code:** A10BB01
- **Approval:** EMA (orphan designation)
- **Use:** Treatment of neonatal diabetes mellitus, for use in newborns, infants and children
- **Benefits:** New formulation, allowing a more accurate dosing in children. In a clinical study glycaemic control remained stable after switching from crushed tablets to oral suspension.
- **Note:** Neonatal diabetes is an extremely rare form of diabetes that is diagnosed in the first six months of life. It is life-threatening and debilitating because of the symptoms caused by high blood sugar levels and the risk of ketoacidosis. This product is the first EMA-approved medicine to treat neonatal diabetes.

**Ertugliflozin for type 2 diabetes**
- **Product names:** Steglatro® (ertugliflozin); Segluromet® (ertugliflozin and metformin hydrochloride); Steglujan® (ertugliflozin and sitagliptin)
- **Dosage form:** Tablet
- **Class:** Ertugliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor; **ATC code:** A10BK04
- **Approval:** FDA, EMA
- **Use:** As an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- **Benefits:** Additional treatment option for type 2 diabetes mellitus
- **Safety information:** Potential adverse events include hypotension, ketoacidosis, acute kidney injury and impairment in renal function, urosepsis and pyelonephritis, lower limb amputation, hypoglycaemia, genital mycotic infections and increased LDL-C levels.

**Velmanase alfa for a rare genetic disorder**
- **Product name:** Lamzede®
- **Dosage form:** Powder for solution for infusion
- **Class:** Recombinant human alpha mannosidase, intravenous enzyme replacement therapy; **ATC code:** A16AB15
- **Approval:** EMA (marketing authorization under exceptional circumstances; orphan designation)
- **Use:** Treatment of non-neurological manifestations of alpha-mannosidosis in patients with a mild to moderate form of the disorder.
- **Benefits:** Decrease of serum oligosaccharide to normal levels observed in a clinical trial, with improved exercise capacity and lung function in some patients.
- **Note:** Alpha-mannosidosis is a rare inherited enzyme disorder that causes cell damage in many organs and tissues. There is currently no cure for this disorder. Patients with early onset severe and rapid progressive disease often do not survive beyond childhood. Those with less severe forms of the disease are managed with supportive care.

**Synthetic human angiotensin II for dangerously low blood pressure**
- **Product name:** Giapreza®
- **Dosage form:** Injection for intravenous infusion
- **Class:** Vasoconstrictor
- **Approval:** FDA (priority review)
Approved

Use: To increase blood pressure in adults with septic or other distributive shock

Benefits: Effective in increasing blood pressure when added to conventional treatments used to raise blood pressure.

Safety information: The product can cause clots in arteries and veins, including deep venous thrombosis, with serious consequences. Prophylactic treatment for blood clots should be used.

► FDA News release, 21 December 2017.

Ozenoxacin for impetigo

Product name: Xepi®

Dosage form: Cream for topical use; ATC code: D06AX14

Class: Quinolone antimicrobial

Approval: FDA

Use: Treatment of impetigo caused by Staphylococcus aureus or Streptococcus pyogenes.

Benefits: More effective than placebo against clinical signs and symptoms of impetigo

► Prescribing information for Xepi®, revised 12/2017.

Hydrocortisone granules for a rare disease in children

Product name: Alkindi®

Dosage form: Granules in capsules for opening

Approval: EMA paediatric-use marketing authorization (PUMA)

Use: Treatment of primary adrenal insufficiency, a rare hormonal disorder in infants, children and adolescents.

Benefits: More accurate dosing of hydrocortisone in children, with a better masking of the bitter taste.

Note: PUMAs can be granted for medicines which are authorized but no longer under patent protection.


Bictegravir, emtricitabine and tenofovir alafenamide for HIV infection

Product name: Biktarvy®

Dosage form: Once-daily fixed-dose combination tablet

Class: Combination of an HIV-1 integrase strand transfer inhibitor (bictegravir) and two HIV-1 nucleoside analog reverse transcriptase inhibitors (emtricitabine and tenofovir alafenamide); ATC code: J05AR20

Approval: FDA (priority review designation)

Use: Treatment of HIV-1 infection in adults ARV-naïve adults or those who are on a stable antiretroviral regimen for at least 3 months with less than 50 HIV-1 RNA copies per mL, no history of treatment failure and no known substitutions associated with resistance to the individual components of this product.

Benefits: Effective new treatment option for a range of patients with HIV-1 infection.

Safety information: Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate, and may occur with discontinuation of this new fixed-dose combination. Liver function should be closely monitored in these patients.

► FDA Prescribing information, revised February 2018.

Ibalizumab for multidrug-resistant HIV infection

Nonproprietary name in the U.S.: ibalizumab-uiyk

Product name: Trogarzo®

Dosage form: Injection for intravenous use

Class: Antiretroviral (ARV); CD4-directed post-attachment inhibitor (first-in-class)

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

Use: In combination with other ARV(s), treatment of heavily treatment-experienced patients with multidrug-resistant HIV-1 infection failing their current ARV regimen.
Approved

**Benefits**: Ability to achieve a significant decrease in HIV-RNA levels in patients who have run out of other HIV treatment options.

**Safety information**: Severe side effects in clinical trials included rash and immune reconstitution syndrome.

► FDA News release, 6 March 2018.

**Baloxavir marboxil** one-dose treatment for influenza

**Product name**: Xofluza®

**Dosage form**: Tablet

**Class**: Cap-dependent endonuclease inhibitor

**Approval**: Ministry of Health, Labour and Welfare (MHLW) of Japan

**Use**: Treatment of influenza types A and B

**Benefits**: Treatment requires only a single oral dose regardless of age.


**Apalutamide** for prostate cancer

**Product name**: Erleada®

**Dosage form**: Tablets

**Class**: Androgen receptor inhibitor

**Approval**: FDA (priority review)

**Use**: Treatment of non-metastatic, castration-resistant prostate cancer

**Benefits**: Significantly longer median metastasis-free survival than with placebo

**Safety information**: Severe side effects include falls, fractures and seizures. Patients with female partners of reproductive potential should be advised to use effective contraception.

**Notes**: This is the first FDA-approved treatment for this condition, and the first to be approved based on the endpoint of metastasis-free survival.

The marketing authorization holder of this product is the first participant in the FDA’s clinical data summary pilot programme (see page 28), which aims to increase transparency on the clinical evidence and decision-making process for FDA-approved products.

► FDA News release, 14 February 2018.

**Burosumab** for a rare bone disease

**Product name**: Crysiva®

**Dosage form**: Solution for injection

**Class**: Human monoclonal antibody that binds to fibroblast growth factor 23 inhibiting its activity; ATC code: M05BX05.

**Approval**: EMA (conditional marketing authorization; orphan designation)

**Use**: Treatment of X-linked hypophosphataemia (XLH) with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons.

**Benefits**: Ability to reduce the loss of phosphate, to improve abnormally low serum phosphate concentrations and other metabolic changes, and to reduce the severity of rickets as shown in x-rays.


**Tezacaftor and ivacaftor** for cystic fibrosis

**Product name**: Symdeko®

**Dosage form**: Co-packed tablets

**Class**: Respiratory system agents; ATC code: R07AX31

**Approval**: FDA

**Use**: Treatment of patients with cystic fibrosis aged 12 years and older who have certain mutations.

**Benefits**: Improvements in lung function and other measures of disease.

► Prescribing information for Symdeko®, Revised 2/2018.

**Netarsudil** to reduce intraocular pressure

**Product name**: Rhopressa®

**Dosage form**: Ophthalmic solution for topical ophthalmic use

**Class**: Rho kinase inhibitor (first-in-class)
Approval: FDA
Use: Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.
Benefits: With once-daily dosing, as effective as twice-daily timolol in reducing intraocular pressure (IOP) in patients with baseline IOP lower than 25mm Hg.

Macimorelin acetate to diagnose growth hormone deficiency
Product name: Macrilen®
Dosage form: Granules for oral solution
Class: Growth hormone (GH) secretagogue receptor agonist; ATC code: V04CD06
Approval: FDA
Use: Diagnosis of adult growth hormone deficiency.
Benefits: More convenient alternative to the insulin tolerance test.
Safety information: Risk of QT interval prolongation, should not be used together with medicines known to prolong QT interval.

Darvadstrocel to treat complex perianal fistulas in Crohn’s disease
Product name: Alofisel®
Dosage form: Suspension for injection
Class: Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue; advanced therapy medicinal product (ATMP)
Approval: EMA (orphan designation)
Use: Treatment of complex perianal fistulas in adult patients with Crohn’s disease
Benefits: Clinically meaningful ability to improve the healing process of complex perianal fistulas.

Voretigene neparvovec for a rare form of inherited vision loss
Non-proprietary name in the U.S.: voretigene neparvovec-rzyl
Product name: Luxturna®
Dosage form: Intraocular suspension for subretinal injection
Class: Adeno-associated virus vector-based gene therapy
Approval: FDA (priority review, breakthrough therapy; orphan drug designation)
Use: Treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy, a rare inherited condition that leads to vision loss and may cause complete blindness in certain patients. Patients must have viable retinal cells as determined by the treating physician(s).
Benefits: Ability to deliver the normal human RPE65 gene to the retinal cells to restore vision.
Note: Analysts expect the marketing authorization holder to announce a price approaching and perhaps exceeding $1 million per person. A U.S.-based non-profit organization has called for the company to disclose its research and development costs for this medicine so that analysts, payers and the public have a basis to assess the company’s pricing decision.(1)

Biosimilars
Insulin glargine
Product name: Semglee®
Reference product: Lantus®
Approval: EMA
Use: Treatment of diabetes mellitus in adults, adolescents and children aged two years and above.
Approved

**Trastuzumab**

**Product name:** Herzuma®

**Reference product:** Herceptin®

**Approval:** EMA

**Use:** Treatment of breast and gastric cancer

- EMA/CHMP Summary of opinion, 14 December 2018.

**Labelling change**

**Nilotinib** – “treatment holiday” possible for certain patients

**Product name:** Tasigna®

**Use:** Treatment of chronic myeloid leukaemia (CML)

**Approval of label change:** FDA (priority review; orphan drug designation)

**Approved change:** Updates to reflect outcomes of clinical trials showing that certain patients may be eligible to stop treatment after a sustained response. This possibility marks a first in the treatment of CML. If treatment is stopped, patients must be regularly monitored for disease recurrence.

- FDA News release, 22 December 2017.

**Extensions of indications**

**Durvalumab** for certain lung cancers

**Product name:** Imfinzi®

**Approval:** FDA (priority review, breakthrough therapy)

**Use:** Treatment of patients with unresectable stage III non-small cell lung cancer and whose cancer has not worsened after treatment with chemotherapy and radiation.

**Benefits:** Ability to extend progression-free survival period after chemoradiation.


**Olaparib** for certain types of breast cancer

**Product name:** Lynparza®

**Approval:** FDA

**Newly approved use:** Treatment of patients with germline breast cancer susceptibility gene (BRCA)-mutated, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been previously treated with chemotherapy. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior hormonal therapy or be considered inappropriate for endocrine treatment.

**Notes:** This is the first poly ADP-ribose polymerase (PARP) inhibitor approved by the FDA to treat breast cancer, and the first approved medicine to treat certain patients with metastatic breast cancer who have a BRCA mutation. The FDA has also expanded the approval of the companion diagnostic BRACAnalysis CDx® to include the detection of BRCA mutations in blood samples from patients with breast cancer.


**Anakinra** for a rare inflammatory disease

**Product name:** Kineret®

**Approval:** EMA

**Newly approved use:** Treatment of Still’s disease in patients aged eight months or older

**Notes:** Still's disease is a rare disease causing inflammation of joints, rash and fever in children and adults. In children, Still’s disease (systemic juvenile idiopathic arthritis) is the most severe form of arthritis. Most patients are initially treated with NSAIDs and glucocorticoids – often in high doses – followed by second line treatment with monoclonal antibodies. Anakinra provides an efficient alternative treatment option.

Publications and events

**Access to medicines**

**Tracking universal health coverage**

Tokyo – A new report from the World Bank and WHO shows that at least half of the world’s population cannot obtain all essential health services, and that the share of people incurring high out-of-pocket medical costs is on the increase.

In 2010 more than 800 million people or 11.7% of the world’s population spent at least 10% of their household budget on health care (up from 9.7% of the world’s population in 2000), and 97 million people were pushed below the poverty line of US$1.90 per day. If the poverty line is set at US$3.10 per day, the number of people impoverished by health spending increased from 105 million (1.7% of the population) in 2000 to 122 million (1.8%) in 2010. On the positive side, some key health services—such as immunization, family planning, antiretroviral treatment and insecticide-treated bed nets to prevent malaria—have become more widely accessible since the turn of the century.

The report was a key point of discussion at the global Universal Health Coverage Forum 2017 in Tokyo, Japan. The Forum in Tokyo is seen as a milestone for accelerating progress towards the target of universal health coverage by 2030.


**Pricing of innovative medicines**

European Union – The European Commission’s Expert Panel on Health has published a new opinion to help guide policy makers in defining new payment models for high-cost innovative medicines that offer meaningful benefits. The report sets out a range of broad principles that could counteract the ever-increasing medicines prices, such as: greater price and cost transparency, use of patent law and market exclusivity rules to promote and reward high-value innovations, and developing and using methods to measure the social value of pharmaceutical products, e.g. in the context of Health Technology Assessment (HTA). (1)

This expert report comes at a time when there is an urgent need to address high medicines prices in Europe. As the European Commission is reviewing current incentives for pharmaceutical innovation, the Expert Panel’s report could be an important contribution to European policy-making on medicines pricing. (2)

A recent paper suggests that the flexibilities in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) are used more often than is commonly assumed, and that they may become increasingly important in making generic medicines more affordable. (3)


Cost prices of essential medicines
New research commissioned by WHO shows that medicines on the Model list of Essential Medicines are often sold at significantly higher prices than those estimated from production costs. Although most medicines on the EML are off-patent, 214 of 277 comparable prices in the UK, 142 of 212 comparable prices in South Africa and 118 of 298 comparable prices in India exceeded the price that would be expected based on cost of production plus a 10% profit margin. The authors conclude that generic price estimation and international price comparisons could empower government price negotiations and support cost-effectiveness calculations.


Benzathine penicillin G shortages
A study has shown that widespread shortages of benzathine benzylpenicillin (benzathine penicillin G) compromise treatment and prevention of syphilis and treatment of other conditions including rheumatic heart disease. Of 95 countries and territories that responded to surveys, 39—including both high-income countries and LMICs—reported a shortage of the medicine. The main reasons are “sole sourcing” of products from a single wholesaler and a single manufacturer, the low price of this sterile injectable medicine compared to its cost of manufacture, and an uncertain demand due to weaknesses in forecasting and procurement. The authors call for viable policy approaches to strengthen procurement infrastructure and support the appropriate treatment of syphilis at the national level. (1)

To identify sources of quality-assured active pharmaceutical ingredient and finished product WHO added benzathine benzylpenicillin to the list of products eligible for prequalification in December 2016. (2)


Medicines quality

Children’s medicines in the DRC
In a cross-sectional survey of paediatric medicines in the Democratic Republic of the Congo, 65 (27.2%) of 239 samples failed to comply with at least one specification. The medicines included amoxicillin (AX) and artemether/lumefantrine (AL) powders for suspension, and paracetamol (PC) tablets. The samples were purchased in the private market in Kinshasa and tested at two accredited laboratories in Belgium. Among the AL samples 59.5% contained less than the specified content of artemether. Significantly more locally manufactured than imported AL- and PC-containing products failed to comply with the specifications set for the survey.
The findings are intended to guide corrective actions by the regulatory authority of the Democratic Republic of Congo, which was the main partner in the research.


**Vaccines**

**CIOMS Guide to vaccine safety communication**

The benefits of immunization for public health have long been recognized. However, no vaccine is completely risk-free. Adverse events will occasionally occur after immunization, and regulators are responsible to inform health professionals and the public about such events. Efficient communication is key for regulatory bodies to maintain trust in their work and in the vaccines that they license.

Although a number of guidance documents exist on how to manage communication on vaccine safety, they do not specifically address the needs of regulatory bodies. To fill this gap, the Council for International Organizations of Medical Sciences (CIOMS) has published its *Guide to Vaccine Safety Communication*. (1)

This new guide offers an overview of strategic communication issues faced by medicines regulators, those responsible for vaccination policies and programmes and other stakeholders when dealing with:

- the launch of newly developed vaccines;
- the introduction of vaccines into new countries, regions or populations; and
- the handling of any safety issues arising during the life cycle of a vaccine.

At a time when vaccine hesitancy—the reluctance to accept immunization—is growing worldwide, this Guide is essential reading for regulators and other stakeholders involved in immunization programmes. It has been prepared by a subgroup of the same multi-skilled group of experts that produced the CIOMS Guide to Active Vaccine Safety Surveillance. (2) With its practical, easy-to-read information, examples and proposed template for a vaccine safety communication plan, the new Guide provides a common ground in a way that has not been achieved otherwise at global level.

Employees of governmental institutions including regulatory bodies, as well as non-profit organizations, can obtain a free PDF of the CIOMS Guide to vaccine safety communication. Please email info@cioms.ch to obtain your free PDF.


**Antimicrobial resistance**

**High resistance levels worldwide**

Bangkok – Data from WHO's new Global Antimicrobial Surveillance System (GLASS) have confirmed the widespread occurrence of antibiotic resistance. The system collects data on eight selected types of bacteria that commonly cause infections in humans. *Mycobacterium tuberculosis* is not included because these data are provided since 1994 in WHO's annual *Global tuberculosis report*.

In response to a first data call, 22 countries provided results from antimicrobial
susceptibility testing (AST) conducted in 2016 on a total of 507,746 isolates, primarily from blood specimens. AST data submission for GLASS involves 12 antimicrobial classes, and 73% of countries provided results for more than half of the antibiotics requested. Resistance patterns for *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* were reported from 17 countries, followed by *Salmonella spp.* (15 countries), *Neisseria gonorrhoeae* (11 countries) and *Shigella spp.* (8 countries).

The findings varied tremendously among reporting countries, but alarmingly high resistance levels were reported to various serious bacterial infections from both high- and low-income countries. The data submitted for this first GLASS report varied in quality and completeness. WHO is supporting countries to set up efficient national antimicrobial resistance surveillance systems.


**Antibiotic use in England**

United Kingdom – At least 20% of all antibiotics prescribed in primary care in England are inappropriate according to data published in a supplement to the Journal of Antimicrobial Chemotherapy. The research found that substantially higher proportions of general practitioner consultations resulted in an antibiotic prescription than is appropriate according to expert opinion: 41% of all consultations for uncomplicated acute cough (target: 10%), 82% for bronchitis (target: 13%), 59% for sore throat (target: 13%), 88% for rhinosinusitis (target: 11%) and 92% for acute otitis media in children (target: 17%).


**Tracking industry action on AMR**

Amsterdam, Davos – The Access to Medicine Foundation has presented its first benchmark report of pharmaceutical companies’ action on antimicrobial resistance (AMR) at the Annual Meeting of the World Economic Forum in Davos, Switzerland. The key findings are summarized below.

There are 28 antibiotics for high-priority pathogens in late stages of development. However, only two of these are supported by plans to ensure that the successful candidate can be made accessible and used appropriately once it reaches the market.

Nearly half of the 30 companies evaluated in the benchmark exercise were involved in efforts to track patterns in antimicrobial resistance, with surveillance programmes running in 147 countries. Pneumonia was the most widely-tracked infection.

Eight companies were setting limits on the levels of antibiotics that can be released into the environment from their manufacturing facilities, although no company made public what is actually released.

Four companies were taking steps to separate sales agents’ bonuses from the volume of antibiotics sold. Two companies had fully implemented this approach, one was piloting it in certain territories, and one was taking steps towards adjusting its sales teams’ incentives.

The Antimicrobial Resistance Benchmark research programme is made possible with
financial support from UK AID and the Dutch Ministry of Health, Welfare and Sport.

Public health updates

Poliovirus:
High stakes in eradication endgame
Geneva – At its 16th meeting the Emergency Committee under the International Health Regulations (2005) (IHR) unanimously agreed that the risk of international spread of poliovirus remains a Public Health Emergency of International Concern with regard to wild poliovirus type 1 (WPV1) and circulating vaccine-derived poliovirus (cVDPV).

The world is closer to polio eradication than ever before in history. A new international spread would be a major setback to achieving eradication.

The Committee advised that its Temporary Recommendations should be extended for a further three months to address the persisting risks of poliovirus spread between Afghanistan and Pakistan, in Nigeria and its Lake Chad neighbours, in countries bordering the Syrian Arab Republic, and in the Democratic Republic of the Congo. The risks are compounded by the global shortage of inactivated polio vaccine, which is causing a lack of type 2 immunity in a growing cohort of children in a number of countries. The Committee requested to be kept updated about the situation in Somalia, where three highly diverged type 2 vaccine-derived polioviruses have been detected in the sewage, suggesting an unreported ongoing transmission.
► WHO Statement, 14 February 2018.

Non-communicable diseases:
New high level commission
Geneva – WHO has announced a new high-level commission on noncommunicable diseases (NCDs). Comprised of heads of state and ministers, leaders in health and development and entrepreneurs, the commission will propose bold and innovative solutions to accelerate prevention and control of NCDs, such as heart and lung disease, cancers, and diabetes.

Seven of every 10 deaths globally each year are from NCDs, which kill more than 15 million people between the ages of 30 and 70 years annually. Low- and lower-middle income countries are increasingly affected, with half of all premature deaths from NCDs occurring in those countries.

The main contributors to NCDs are tobacco use, harmful use of alcohol, unhealthy diets, and physical inactivity.
Many lives can be saved through prevention, early diagnosis and improved access to quality and affordable treatment. WHO has called for a whole-of-government approach to reduce the main risk factors. In 2017 the World Health Assembly had endorsed the set of WHO “best buys” to prevent or delay most premature NCD deaths.

The new commission runs until October 2019. It will provide actionable recommendations to the Third United Nations General Assembly High-level Meeting on NCDs, scheduled for the second half of 2018.

Cholera:
WHO responds to outbreaks
Lusaka – The Government of Zambia has launched a campaign to immunize 1 million people against cholera with support from WHO and partners. This is in response
to an unusually high number of seasonal cholera cases, with 2672 cases and 63 deaths reported since October 2017. Most of the cases occurred in the capital Lusaka. A further one million people living in known cholera hotspots across the country are to be vaccinated later in 2018. WHO is also working with the Zambia National Public Health Institute to address the underlying causes of the outbreak, track down cases, treat cholera patients and provide community health education.(1)

Juba – In South Sudan, the end of the longest and largest cholera outbreak was declared on 7 February. The outbreak had been declared in June 2016; the last person with confirmed cholera case was discharged in December 2017. By that time over 20,000 suspected cholera cases and 436 deaths had been reported. The government worked with a range of partners to enhance surveillance, deploy rapid response teams, provide clean water, promote good hygiene practices and treat cholera patients. In 2017 more than 885,000 people at risk were immunized with oral cholera vaccine sourced from the global stockpile funded by Gavi, The Vaccine Alliance. Despite security challenges, nearly 500,000 people received a second dose of the vaccine.

► (1) WHO Regional Office for Africa. News. 10 January 2018.  
(2) WHO Regional Office for Africa. News. 7 February 2018.

Lassa fever: Largest-ever outbreak in Nigeria

Abuja – Nigeria is fighting its largest outbreak of Lassa fever on record. Between 1 January and 4 February 2018 nearly 450 suspected cases of Lassa fever were reported, of which 132 were confirmed by laboratory testing.(1) By 28 February that number had increased to 317 laboratory-confirmed cases, and 72 deaths have been recorded. The outbreak has spread to 18 states, with the hot spots being the southern states of Edo, Ondo and Ebonyi.(2)

Lassa fever is an acute viral haemorrhagic fever endemic to West Africa. Benin, Liberia and Sierra Leone have also reported recent cases. WHO is supporting Nigeria and Benin in surveillance activities, infection control and prevention, and is working with countries in the region to strengthen coordination and cross-border cooperation.


WHO prequalification updates

First typhoid conjugate vaccine prequalified

At the end of December 2017, WHO prequalified the first conjugate vaccine for typhoid, Bharat Biotech’s Typbar-TCV®. Typhoid conjugate vaccines are innovative products that have longer-lasting immunity than older vaccines, require fewer doses and can be given to young children. In October 2017, the Strategic Advisory Group of Experts (SAGE) on immunization recommended typhoid conjugate vaccine for routine use in children over 6 months of age in typhoid-endemic countries. This vaccine will help to reduce the continuing high burden of typhoid fever and the consequent frequent use of antibiotics which has led to an alarming increase in antimicrobial resistance to Salmonella typhi.

Other “firsts”

- First dolutegravir active pharmaceutical ingredient prequalified. Dolutegravir is used for the manufacture of medicines to treat HIV/AIDS.
- First dispersible paediatric levofloxacin tablets (TB326) prequalified. This product is used for treatment of multi-drug resistant tuberculosis in children.
- First rectal artesunate (MA124) prequalified. This product is used to treat severe malaria in children.

Guidance on dossier deficiencies

The Prequalification Team has published additional guidance for manufacturers on common deficiencies in finished pharmaceutical product (FPP) dossiers with respect to: The active pharmaceutical ingredient (API) supplier versus the FPP manufacturer’s API specifications, control of polymorph identity and particle size distribution, control of related substances in APIs and FPPs, granulation processes, hold times, dissolution profiles and quality control testing limits, control of moisture content in final blend and finished solid oral products, and process validation.

- WHO Prequalification of medicines. List of prequalified finished pharmaceutical products.

Upcoming event

18th ICDRA

The 18th International Conference of Drug Regulatory Authorities (ICDRA) will take place in Dublin, Ireland, on 3–7 September 2018. The theme of the conference is Smart Safety surveillance: A life-cycle approach to promoting safety of medical products. The pre-ICDRA event will be convened from 3–4 September and is open to all interested stakeholders. The conference itself will be held on 5–7 September and is open to representatives of governments and national regulatory authorities only.

Since 1980, ICDRA has brought together regulatory authorities from WHO Member States to strengthen collaboration and develop international consensus on regulatory priorities. This biennial conference provides a unique forum to support and guide regulatory authorities, WHO and international stakeholders. Some of this year’s topics include a look back at the 17th ICDRA recommendations and their implementation, future directions of the WHO prequalification programme, strategic approaches to improving access to medical products, and the safety of medical products throughout their life cycle.

- 18th ICDRA website: http://www.icdra2018.ie/
Consultation documents

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

The International Pharmacopoeia

Moxifloxacin hydrochloride
(Moxifloxacini hydrochloridum)

This is a draft proposal of a monograph for The International Pharmacopoeia (Working document QAS/16.651, January 2018). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

[Note from the Secretariat. The proposed monograph is based on information found in Ph.Eur. 8.0, Pharmeuropa 29.3, USP 39 and the Indian Pharmacopoeia 2014, in the scientific literature, submitted by pharmaceutical manufacturers, and on laboratory investigations performed by a WHO Collaborating Centre and a collaborating laboratory. The monograph is proposed for inclusion in The International Pharmacopoeia.]

Molecular formula. $\text{C}_{21}\text{H}_{25}\text{ClF}_3\text{N}_3\text{O}_4\cdot\text{H}_2\text{O}$

Relative molecular mass. 455.9.

Graphic formula

Chemical name. 1-Cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride monohydrate; CAS Reg. No. 192927-63-2 (monohydrate).

Description. A light yellow or yellow powder or crystals.

Solubility. Sparingly soluble in water R, slightly soluble in ethanol (~760 g/L) TS, practically insoluble in acetone R.
Category. Antibacterial, antituberculosis.

Storage. Moxifloxacin hydrochloride should be kept in tightly closed containers, protected from light.

Labelling. The designation on the container of Moxifloxacin hydrochloride should state the substance is in the form of the monohydrate.

Additional information. Moxifloxacin hydrochloride may exhibit polymorphism.

Requirements

Definition. Moxifloxacin hydrochloride contains not less than 98.0% and not more than 102.0% (“Assay”, method A) or not less than 99.0% and not more than 101.0% (“Assay”, method B) of $C_{21}H_{25}ClFN_3O_4$, calculated with reference to the anhydrous substance.

Manufacture. The production method is validated to demonstrate the satisfactory enantiomeric purity of the final product.

Identity tests

- Either tests A, C and D or 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 is concordant with the spectrum obtained from moxifloxacin hydrochloride RS or the reference spectrum of moxifloxacin hydrochloride. If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the test substance and moxifloxacin hydrochloride RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from moxifloxacin hydrochloride RS.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 4 volumes of 1-butanol R, 4 volumes of methanol R and 2 volumes of ammonia (~100 g/L) TS as the mobile phase. Apply separately to the plate 10 µL of each of the following two solutions. For solution (A) dissolve a quantity of the test substance in methanol R to give a solution containing 1 mg of the test substance per mL. Dilute a portion of the solution with methanol R to give a solution containing 0.05 mg of the test substance per mL. For solution (B) use an approximately 0.05 mg/mL solution of moxifloxacin hydrochloride RS in methanol R. Develop the plate for a distance of 15 cm. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of air. Examine the chromatogram under ultraviolet light (366 nm). The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to moxifloxacin in the chromatogram obtained with solution (B).

C. Prepare a solution of 50 mg of the test substance in 5 mL of water R, add 1 mL of nitric acid (~130 g/L) TS, mix, allow to stand for 5 minutes and filter. The filtrate yields reaction A described under 2.1 General identification tests as characteristic of chlorides.
D. Determine the specific optical rotation (1.4) using a solution of 0.200 g in 20.0 mL of a mixture of equal volumes of acetonitrile R and water R. Calculate with reference to the anhydrous substance; the specific optical rotation is between -125 to -138.

Clarity and colour of solution. Dissolve 1.0 g of the test substance in 20 mL of sodium hydroxide (~85 g/L) TS. The solution is not more intensely coloured than reference solution GY₂ (1.11.2, Method II).

pH value (1.13). pH of a 2 mg/mL solution in carbon-dioxide-free water R, 3.9 to 4.6.

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, 30 mL anhydrous methanol and 3 minutes stirring before titration starts; the water content is not more than 45 mg/g.

Sulfated ash (2.3). Not more than 1.0 mg/g, determined on 1.0 g in a platinum crucible.

Related substances. Perform the test in subdued light, preferably using low-actinic glassware.

Carry out the tests as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded phenylsilyl groups (5 µm).¹

Use the following mobile phase: Mix 28 volumes of methanol R and 72 volumes of a solution containing 0.5 g/L of tetrabutylammonium hydrogen sulfate R, 1.0 g/L of potassium dihydrogen phosphate R and 3.4 g/L of phosphoric acid (~1440 g/L) TS.

Operate with a flow rate of 1.3 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 293 nm. Maintain the column temperature at 45°C.

Prepare solvent (A) by dissolving 0.50 g of tetrabutylammonium hydrogen sulfate R and 1.0 g of potassium dihydrogen phosphate R in about 500 mL of water R. Add 2 mL of phosphoric acid (~1440 g/L) TS and 0.050 g of anhydrous sodium sulfite R, then dilute to 1000.0 mL with water R.

Prepare the following solutions in solvent (A). For solution (1) dissolve about 50.0 mg of the test substance and dilute to 50.0 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) use a solution containing about 1 mg of moxifloxacin for peak identification RS (containing moxifloxacin and the impurities A, B, E and F) per mL.

Inject alternately 10 µL of solution (1), (2) and (3). Record the chromatograms for about 2.5 times the retention time of moxifloxacin.

Use the chromatogram supplied with moxifloxacin for peak identification RS and the chromatogram obtained with solution (3) to identify the peaks due to impurities A, B, E and F in the chromatogram obtained with solution (1). The impurities, if present, are eluted at the following relative retention with reference to moxifloxacin (retention time about 11 to 14 minutes): impurity F about 0.9; impurity A about 1.1; impurity B about 1.3; and impurity E about 1.7.

¹ An Inertsil Ph and a Zorbac Eclipse XDB-Phenyl column were found suitable.
The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peak due to moxifloxacin and the peak due to impurity A is at least 1.5 and the chromatogram obtained is similar to the chromatogram supplied with moxifloxacin for peak identification RS.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.4, is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.1%);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 3.5, is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.1%);
- the area of any peak corresponding to impurity F is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.1%);
- the area of any other impurity peak is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.10%);
- the sum of the corrected areas of any peak corresponding to impurity B and E and the areas of all other impurity peaks is not greater than 3 times the area of the peak due to moxifloxacin obtained with solution (2) (0.3%). Disregard any peak with an area less than 0.5 times the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.05%).

**Assay**

- Either test A or test B may be applied.

**A.** Carry out the test as described under 1.14.4 *High-performance liquid chromatography* using the conditions given under "Related substances".

Prepare the following solutions in solvent (A). For solution (1) dissolve 50.0 mg of the substance to be examined and dilute to 50.0 mL. Dilute 2.0 mL of this solution to 20.0 mL. For solution (2) dissolve 50.0 mg of moxifloxacin hydrochloride RS and dilute to 50.0 mL. Dilute 2.0 mL of this solution to 20.0 mL.

Inject alternately 10 µL of solution (1) and (2).

Measure the areas of the peaks corresponding to moxifloxacin obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of C_{21}H_{25}ClFN_{3}O_{4}, using the declared content of C_{21}H_{25}ClFN_{3}O_{4} in moxifloxacin hydrochloride RS.

**B.** Dissolve about 0.320 g, accurately weighed, in 50 mL of water R. Titrate with sodium hydroxide (0.1 mol/L) VS, determining the end-point potentiometrically. Read the volume added to reach the first point of inflection. Each mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 43.79 mg of C_{21}H_{25}ClFN_{3}O_{4}. 

**Moxifloxacin hydrochloride (Ph. Int.)**
Moxifloxacin hydrochloride (Ph. Int.)

**Impurities**

A. 1-cyclopropyl-6,8-difluoro-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [*synthesis-related impurity*]

B. 1-cyclopropyl-6,8-dimethoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [*synthesis-related impurity*]

C. 1-cyclopropyl-8-ethoxy-6-fluoro-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [*synthesis-related impurity*]

D. 1-cyclopropyl-8-fluoro-6-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [*synthesis-related impurity*]
E. 1-cyclopropyl-6-fluoro-8-hydroxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [synthesis-related impurity]

F. 1-cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [synthesis-related impurity]

G. methyl 1-cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylate [synthesis-related impurity]

**Reagent to be established**

**Sodium hydroxide (~85 g/L) TS**
A solution of sodium hydroxide R in water R containing about 85 g/L of NaOH.

**Sodium sulfite, anhydrous R**
Anhydrous sodium sulfite of a suitable quality should be used.

***
Moxifloxacin tablets
(Moxifloxacini compressi)

This is a draft proposal of a monograph for The International Pharmacopoeia (Working document QAS/16.650, January 2018). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

[Note from the Secretariat. The proposed monograph is based on information provided by the British Pharmacopoeia and pharmaceutical manufacturers, found in the scientific literature, and on laboratory investigations. The monograph is proposed for inclusion in The International Pharmacopoeia.]

Category. Antibacterial, antituberculosis.

Labelling. The designation on the container of moxifloxacin tablets should state that the active ingredient is Moxifloxacin hydrochloride and the quantity should be indicated in terms of equivalent amount of moxifloxacin.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML) 400 mg per tablet. Strength in the current WHO EML for children: 400 mg per tablet.

Requirements

Comply with the monograph for Tablets.

Definition. Moxifloxacin tablets contain Moxifloxacin hydrochloride. They contain not less than 90.0% and not more than 110.0% of the amount of moxifloxacin (C₂₁H₂₄FN₃O₄) stated on the label.

Identity tests

• Either test A or test B may be applied.

A. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 4 volumes of 1-butanol R, 2 volumes of methanol R and 2 volumes of ammonia (~100 g/L) TS as the mobile phase. Apply separately to the plate 10 µL of each of the following two solutions. For solution (A) shake a quantity of the powdered tablets, equivalent to about 20 mg of moxifloxacin, with 20 mL of methanol R and filter. Dilute 1 mL of the filtrate to 20 mL with methanol. For solution (B) use an approximately 0.055 mg/mL solution of moxifloxacin hydrochloride RS in methanol R. Develop the plate for a distance of 15 cm. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of air. Examine the chromatogram under ultraviolet light (366 nm). The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to moxifloxacin in the chromatogram obtained with solution (B).

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”. The retention time of the principal peak in the
chromatogram obtained with solution (1) corresponds to the retention time of the peak due to moxifloxacin in the chromatogram obtained with solution (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 hydrochloric acid (~3.65 g/L) TS and rotating the paddle at 50 revolutions per minute. At 30 minutes withdraw a sample of 10.0 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 resulting solution, suitably diluted with the dissolution medium, if necessary, at the maximum at about 295 nm, using the dissolution medium as the blank. Measure at the same time and under the same conditions the absorbance of a suitable solution of moxifloxacin hydrochloride RS in the dissolution medium.

For each of the tablets calculate the total amount of moxifloxacin \((C_{21}H_{24}FN_3O_4)\) in the medium. Each mg of moxifloxacin hydrochloride \((C_{21}H_{25}ClFN_3O_4)\) is equivalent to 0.917 mg of moxifloxacin \((C_{21}H_{24}FN_3O_4)\).

Evaluate the results as described under 5.5 Dissolution test for solid oral dosage forms,

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

**Note from the Secretariat.** It is intended to determine the absorptivity value of moxifloxacin during the establishment of moxifloxacin hydrochloride RS. The value will then be included in the test description.

**Related substances.** Perform the test in subdued light, preferably using low-actinic glassware.

Carry out the tests as described under 1.14.4 High-performance liquid chromatography using a stainless steel column \((25 \text{ cm} \times 4.6 \text{ mm})\) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded phenylsilyl groups \((5 \mu \text{m})\).\(^1\)

Use the following mobile phase: mix 28 volumes of methanol R and 72 volumes of a solution containing 0.5 g/L of tetrabutylammonium hydrogen sulfate R, 1.0 g/L of potassium dihydrogen phosphate R and 3.4 g/L of phosphoric acid \((~1440 \text{ g/L})\) TS.

Operate with a flow rate of 1.3 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 293 nm. Maintain the column temperature at 45°C.

Prepare solvent by dissolving 0.50 g of tetrabutylammonium hydrogen sulfate R and 1.0 g of potassium dihydrogen phosphate R in about 500 mL of water R. Add 2 mL of phosphoric acid \((~1440 \text{ g/L})\) TS and 0.050 g of anhydrous sodium sulfite R, then dilute to 1000.0 mL with water R.

Prepare the following solutions in solvent (A). For solution (1) dissolve a quantity of the powdered tablets, equivalent to about 100 mg of moxifloxacin in 100 mL of solvent (A) with sonication and filter. For solution (2) dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of this solution to 10 volumes. For solution (3) use a solution containing about 1 mg of moxifloxacin for peak identification RS (containing moxifloxacin and the impurities A, B, E and F) per mL.

Inject alternately 10 µL of solution (1), (2) and (3). Record the chromatograms for about 2.5 times the retention time of moxifloxacin.

\(^1\) A Zorbax Eclipse XDB-Phenyl column was found suitable.
Moxifloxacin tablets (Ph. Int.)

Use the chromatogram supplied with moxifloxacin for peak identification RS and the chromatogram obtained with solution (3) to identify the peaks due to impurities A, B and E in the chromatogram obtained with solution (1). The impurities, if present, are eluted at the following relative retention with reference to moxifloxacin (retention time about 11 to 14 minutes): impurity A about 1.1; impurity B about 1.3; impurity E about 1.7.

The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peak due to moxifloxacin and the peak due to impurity A is at least 1.5 and the chromatogram obtained is similar to the chromatogram supplied with moxifloxacin for peak identification RS.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.4, 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 3.5, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the area of any other impurity peak is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
- the sum of the areas of all impurity peaks is not greater than 10 times the area of the principal peak obtained with solution (2) (1.0%). Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Assay. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Related substances”.

Prepare the following solutions in solvent (A). For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets, accurately weighed, containing the equivalent of about 500 mg of moxifloxacin into a 500 mL volumetric flask. Add 400 mL of solvent (A), sonicate for 30 minutes, dilute to volume and filter. Dilute 1 volume of the filtrate to 10 volumes. For solution (2) use a solution containing about 0.11 mg moxifloxacin hydrochloride RS, accurately measured, per mL.

Inject alternately 10 µL of solution (1) and (2).

Measure the areas of the peaks corresponding to moxifloxacin obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of \( \text{C}_{21}\text{H}_{24}\text{FN}_{3}\text{O}_{4} \) in the tablets using the declared content of \( \text{C}_{21}\text{H}_{25}\text{ClFN}_{3}\text{O}_{4} \) in moxifloxacin hydrochloride RS. Each mg of \( \text{C}_{21}\text{H}_{25}\text{ClFN}_{3}\text{O}_{4} \) is equivalent to 0.917 mg of moxifloxacin (\( \text{C}_{21}\text{H}_{24}\text{FN}_{3}\text{O}_{4} \)).

Impurities

The impurities limited by the requirements of this monograph include the impurities listed in the monograph for Moxifloxacin hydrochloride.

***
Clindamycin palmitate hydrochloride
*(Clindamycini palmitas hydrochloridum)*

This is a draft proposal of a monograph for *The International Pharmacopoeia* (Working document QAS/16.654/Rev.1, February 2018). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

**Molecular formula.** $C_{34}H_{63}ClN_2O_6S\cdot HCl$

**Relative molecular mass.** 699.85

**Graphic formula**

![Graphic formula image]

**Chemical name.** L-threo-α-D-galacto-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[1-methyl-4-propyl-2-pyrrolidinyl]-carbonyl]amino]-1-thio-2-hexadecanoate, monohydrochloride, (2S-trans); Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-palmitate monohydrochloride; CAS Reg. No. 25507-04-4.

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

**Solubility.** Freely soluble in ethanol and in dichloromethane; soluble in water.

**Category.** Antibacterial.

**Storage.** Clindamycin palmitate hydrochloride should be preserved in a tightly closed container.

**Additional information.** Clindamycin palmitate hydrochloride is a semi-synthetic product derived from a fermentation product.

**Requirements**

**Definition.** Clindamycin palmitate hydrochloride contains not less than 91.0% and not more than 102.0% of $C_{34}H_{63}ClN_2O_6S\cdot HCl$, calculated with reference to the anhydrous substance.

**Identity tests**

Either test A alone or tests B and C may be applied.
Clindamycin palmitate hydrochloride (Ph. Int.)

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 clindamycin palmitate hydrochloride RS or with the reference spectrum of clindamycin palmitate hydrochloride.

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

C. A 10 mg/mL solution yields reaction B described under 2.1 General identification tests as characteristic of chlorides.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A. Use 0.1 g of the test substance. The water content is not more than 30 mg/g.

pH value (1.13). pH of a 10 mg/mL solution in carbon-dioxide-free water R, 2.8–3.8.

Sulfated ash (2.3). Not more than 5 mg/g.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 μm).\(^1\)

Use the following conditions for gradient elution:

- mobile phase A: Ammonium acetate (~0.40 g/L) TS - acetonitrile R (50:50);
- mobile phase B: Acetonitrile R.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Mobile phase A (%) v/v</th>
<th>Mobile phase B (%) v/v</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–30</td>
<td>100 to 0</td>
<td>0 to 100</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>30–80</td>
<td>0</td>
<td>100</td>
<td>Isocratic</td>
</tr>
<tr>
<td>80–81</td>
<td>0 to 100</td>
<td>100 to 0</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>81–90</td>
<td>100</td>
<td>0</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Prepare the following solutions in methanol R. For solution (1) dissolve about 100 mg of clindamycin palmitate hydrochloride and dilute to 10.0 mL. For solution (2) dilute 2.0 mL of solution (1) to 100 mL. For solution (3) dissolve about 75 mg clindamycin palmitate hydrochloride RS (containing clindamycin palmitate hydrochloride and impurity A) and dilute to 10.0 mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 230 nm.

Inject alternately 20 μL each of solution (1), (2) and (3).

In the chromatogram obtained with solution (3) the retention time of clindamycin palmitate is about 37 minutes. The test is not valid unless the resolution between the peaks due to clindamycin palmitate and impurity A (relative retention about 0.9) is at least 3.0.

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\(^1\) Agilent\textsuperscript{®} Zorbax Eclipse XDB-C8 has been found suitable.
In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to clindamycin palmitate: impurity B about 0.8 and impurity A about 0.9.

In the chromatogram obtained with solution (1):

- the area of any impurity peak is not more than the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);
- the sum of the areas of all impurity peaks is not more than 3.5 times the area of the principal peak in the chromatogram obtained with solution (2) (7.0%). Disregard any peak with an area less than 0.025 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

**Assay.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 μm).²

As the mobile phase, use a mixture of 10 volumes of ammonium acetate (~0.40 g/L) TS and 90 volumes of acetonitrile R.

Prepare the following solutions in mobile phase. For solution (1) transfer about 50 mg of the test substance, accurately weighed, into a 50 mL volumetric flask, dissolve and dilute to volume. For solution (2) dissolve about 50 mg of clindamycin palmitate hydrochloride RS and dilute to 50.0 mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 230 nm.

Inject alternately 20 μL each of solutions (1) and (2) and record the chromatograms for about 40 minutes.

Measure the areas of the peak responses corresponding to clindamycin palmitate obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of clindamycin palmitate hydrochloride (C₃₄H₆₃ClN₂O₆S.HCl), using the declared content of clindamycin palmitate hydrochloride (C₃₄H₆₃ClN₂O₆S.HCl) in clindamycin palmitate hydrochloride RS.

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² Waters Symmetry C8 column has been found suitable.
Clindamycin palmitate hydrochloride (Ph. Int.)

Impurities

A. L-threo-α-D-galacto-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[1-methyl-4-ethyl-2-pyrrolidinyl]-carbonyl]amino]-1-thio-2-hexadecanoate, (2S-trans)-; Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-ethyl-L-2-pyrrolidine carboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-palmitate (clindamycin B palmitate) (synthesis-related impurity)

B. L-threo-α-D-galacto-Octopyranoside, methyl-epimer-7-chloro-6,7,8-trideoxy-6-[[1-methyl-4-propyl-2-pyrrolidinyl]-carbonyl]amino]-1-thio-2-hexadecanoate, (2S-trans)-; Methyl-epimer-7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-palmitate; (7-epiclindamycin 2-palmitate) (synthesis-related impurity)

Reagents to be established

Ammonium acetate (~0.40 g/L) TS
A solution of ammonium acetate R containing about 0.385 g of C₂H₇NO₂ per litre (approximately 0.005 mol/L).

Docusate sodium R
C₂₀H₃₇NaO₇S
A commercially available reagent of suitable grade.

***
Clindamycin palmitate powder for oral solution
(\textit{Clindamycini palmitas pulvis pro solutione perorali})

This is a draft proposal of a monograph for \textit{The International Pharmacopoeia} (Working document QAS/16.655, February 2018). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

\textbf{Category.} Antibacterial.

\textbf{Storage.} Clindamycin palmitate powder for oral solution should be kept in a tightly closed container.

\textbf{Additional information.} Strength in the current WHO Model List of Essential Medicines (EML): 75 mg/5 mL (as palmitate). Strengths in the current WHO EML for Children: 75 mg/5 mL (as palmitate).

Clindamycin palmitate powder for oral solution may contain excipients that are suspended in the reconstituted solution. Shake until the solution is uniform.

\textbf{Labelling.} The designation on the container of clindamycin palmitate powder for oral solution should state that the active ingredient is clindamycin palmitate hydrochloride and the quantity should be indicated in terms of equivalent amount of clindamycin.

\textbf{Requirements}

Complies with the monograph for \textit{Liquid preparations for oral use}; the powder complies with the section of the monograph entitled \textit{Powders for oral solutions, oral suspensions and oral drops}.

\textbf{Definition.} Clindamycin palmitate powder for oral solution is a solution of Clindamycin palmitate hydrochloride in a suitable vehicle, which may be flavoured. It is prepared from the powder as stated on the label before use. When freshly constituted the oral solution contains not less than 90.0\% and not more than 110.0\% of the labelled amount of clindamycin (\textit{C}_{18}\textit{H}_{33}\textit{ClN}_{2}\textit{O}_{5}\textit{S}).

\textbf{Identity test}

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

\textbf{pH value} (1.13). pH of a solution constituted as directed in the labelling, 2.5–5.0.

\textbf{Loss on drying.} Dry the powder for oral solution to constant mass at 60\°C under reduced pressure; it loses not more than 20 mg/g.
Clindamycin palmitate powder for oral solution (Ph. Int.)

Related substances

Use the oral solution immediately after preparation.

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 μm).1

Use the following conditions for gradient elution:
- mobile phase A: Ammonium acetate (~0.40 g/L) TS – acetonitrile R (50:50);
- mobile phase B: Acetonitrile R.

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<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–30</td>
<td>100 to 0</td>
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</tr>
<tr>
<td>81–90</td>
<td>100</td>
<td>0</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>
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Prepare the following solutions in methanol R. For solution (1) transfer a quantity of the oral solution, equivalent of about 57 mg of clindamycin to a 10 mL volumetric flask and dilute to volume. For solution (2) dilute 2.0 mL of solution (1) to 100.0 mL. For solution (3) dissolve about 75 mg clindamycin palmitate hydrochloride RS (containing clindamycin palmitate hydrochloride and impurity A) and dilute to 10.0 mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 230 nm.

Inject alternately 20 μL each of solution (1), (2) and (3).

In the chromatogram obtained with solution (3) the retention time of clindamycin palmitate is about 37 minutes. The test is not valid unless the resolution between the peaks due to clindamycin palmitate and impurity A (relative retention about 0.9) is at least 3.0.

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to clindamycin palmitate: impurity B about 0.8 and impurity A about 0.9.

In the chromatogram obtained with solution (1):
- the area of any impurity peak is not more than the area of the principal peak in the chromatogram obtained with solution (2) (2.0%);
- the sum of the areas of all impurity peaks is not more than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (8.0%). Disregard any peak with an area less than 0.025 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

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1 Agilent® Zorbax Elipse XDB-C8 (4.6 x 250 mm, 5 μm) has been found suitable.
**Assay.** Use the oral solution immediately after preparation.

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).

As the mobile phase, use a mixture of 10 volumes of ammonium acetate (~0.40 g/L) TS and 90 volumes of acetonitrile R.

Prepare the following solutions in mobile phase. For solution (1) dissolve a quantity of the oral solution, equivalent to about 30 mg of clindamycin, accurately weighed, and dilute to 50.0 mL, filter and use the filtrate. For solution (2) dissolve about 50 mg clindamycin palmitate hydrochloride RS and dilute to 50.0 mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 230 nm.

Inject alternately 20 μL each of solutions (1) and (2) and record the chromatograms for about 40 minutes.

Measure the areas of the peak responses corresponding to clindamycin palmitate obtained in the chromatograms from solutions (1) and (2). Determine the weight per mL (1.3.1) of the oral solution and calculate the percentage content of clindamycin (C₁₈H₃₃ClN₂O₅S) in the oral solution, using the declared content of clindamycin palmitate hydrochloride (C₃₄H₆₃ClN₂O₆S.HCl) in clindamycin palmitate hydrochloride RS. Each mg of clindamycin palmitate hydrochloride (C₃₄H₆₃ClN₂O₆S.HCl) is equivalent to 0.607 mg clindamycin (C₁₈H₃₃ClN₂O₅S).

**Impurities**

The impurities limited by the requirements of this monograph include those listed in the monograph for Clindamycin palmitate hydrochloride.

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2 Waters Symmetry C8 has been found suitable.
Amoxicillin trihydrate
*(Amoxicillinum trihydricum)*

This is a draft proposal of a revised monograph for *The International Pharmacopoeia* (Working document QAS/16.680, February 2018). The working document with line numbers and tracked changes is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

[Note from the Secretariat. It is proposed to revise the monograph on Amoxicillin trihydrate of The International Pharmacopoeia. The revision is based on laboratory investigations and on information found in the European Pharmacopoeia and the United States Pharmacopeia. Comments are in particular sought regarding the nature of the impurities listed on the transparency list, i.e. whether they are synthesis-related impurities, degradation products or both. Changes for the monograph available on the above-mentioned website are indicated in the text by insert or delete.]

C₁₆H₁₉N₃O₅S₃H₂O

Relative molecular mass. 419.5

**Chemical name.** (2S,5R,6R)-6-[(2R)-2-Amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate; (-)-6-[2-Amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate; (2S,5R,6R)-6-[(R)-2-amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate; 6-[amino(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate; CAS Reg. No. 61336-70-7.

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

**Solubility.** Slightly soluble in water and methanol R; very slightly soluble in ethanol (~750 g/L) TS, practically insoluble in fatty oils.

**Category.** Antibacterial.

**Storage.** Amoxicillin trihydrate should be kept in a tightly closed container.

**Additional information.** Amoxicillin trihydrate is a semi-synthetic product derived from a fermentation product.
Amoxicillin trihydrate (Ph. Int.)

Requirements

**Definition.** Amoxicillin trihydrate contains not less than 95.0% and not more than 102.0% of C₁₆H₁₉N₃O₅S, calculated with reference to the anhydrous substance.

**Manufacture.** The method of production is validated to demonstrate that the substance, if tested, would comply with a limit of not more than 20 µg/g of N,N-dimethylaniline using a suitable method.

**Identity tests**

- Either test A alone or tests B and C or test 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 is concordant with the spectrum obtained from amoxicillin trihydrate RS or with the reference spectrum of amoxicillin trihydrate.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silanized silica gel R3 as the coating substance and a mixture of 9 volumes of a solution containing 15.4 g of ammonium acetate R in 100 mL, the pH of which has been adjusted to 5.0 with glacial acetic acid R, and 1 volume of acetone R as the mobile phase. Apply separately to the plate 1 µL of each of 3 solutions in sodium hydrogen carbonate (40 g/L) TS containing (A) 2.5 mg of the test substance per mL, (B) 2.5 mg of amoxicillin trihydrate RS per mL and (C) a mixture of 2.5 mg of amoxicillin trihydrate RS and 2.5 mg of ampicillin trihydrate RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air until the solvents have evaporated. Expose the plate to iodine vapours until the spots appear 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 valid only if the chromatogram obtained with solution (C) shows two clearly separated spots.

C. Place about 2 mg of the test substance in a test-tube (150 mm × 15 mm), moisten with 1 drop of water and add about 2 mL of sulfuric acid (~1760 g/L) TS. Mix the contents of the tube by swirling; the solution remains practically colourless. Place the tube in a water-bath for 1 minute; a dark yellow colour develops.

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

**Specific optical rotation** (1,4). Use a 2.0 mg/mL of the test substance solution in carbon-dioxide-free water R and calculate with reference to the anhydrous substance; \([\alpha]_D^{20} = +290\) to +315.

**Solution in hydrochloric acid and ammonia.** Prepare a solution of 1.0 g in 10 ml of hydrochloric acid (0.5 mol/l) VS. Prepare a second solution of 1.0 g in 10 ml of ammonia (~100 g/l) TS. Examine both solutions immediately.

Neither of these solutions are more opalescent than opalescence standard TS3.
Amoxicillin trihydrate (Ph. Int.)

**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 20 µg/g.

**Sulfated ash (2.3).** Not more than 10 mg/g.

**Water.** Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using about 0.1 g of the test substance; the water content is not less than 0.115 g/g and not more than 0.145 g/g.

**pH value (1.13).** pH of a 2mg/mL solution in carbon-dioxide-free water R, 3.5–5.5.

**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).

Prepare the following buffer solution pH 5.0. Adjust the pH of 250 mL of potassium dihydrogen phosphate (27.2 g/L) TS with sodium hydroxide (~80 g/L) TS to 5.0 and dilute to 1000 mL with water R.

Use the following conditions for gradient elution:
- mobile phase A: 1 volumes of acetonitrile R and 99 volumes of buffer solution pH 5.0;
- mobile phase B: 20 volumes of acetonitrile R and 80 volumes of buffer solution pH 5.0.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
</tr>
</thead>
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<td>0 to (t_R)</td>
<td>92</td>
<td>8</td>
<td>Isocratic</td>
</tr>
<tr>
<td>(t_R) to ((t_R+25))</td>
<td>92 to 0</td>
<td>8 to 100</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>((t_R+25)) to ((t_R+40))</td>
<td>0</td>
<td>100</td>
<td>Isocratic</td>
</tr>
<tr>
<td>((t_R+40)) to ((t_R+55))</td>
<td>0 to 92</td>
<td>100 to 8</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>((t_R+55)) to ((t_R+70))</td>
<td>92</td>
<td>8</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

\(t_R\) = retention time of amoxicillin determined with solution (2)

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Prepare the following solutions immediately before use in mobile phase A. For solution (1) dissolve about 30 mg of the test substance and dilute to 20.0 mL. For solution (2) dilute 2.0 mL of solution (1) to 20.0 mL. Dilute 2.0 mL of this solution to 20.0 mL. For solution (3) dissolve 4.0 mg of cefadroxil R and dilute to 50.0 mL. To 5.0 mL of this solution add 2.0 mL of solution (1) and dilute to 100.0 mL.

Inject 50 µL of solution (3). The test assay is not valid unless in the chromatogram the resolution between the peaks due to amoxicillin and cefadroxil is at least 2.0.

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

---

1 Agilent® Xbridge C18 column (4.6×250 mm, 5 µm) was found suitable.
In the chromatogram obtained with solution (1):

- the area of any impurity peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

**Assay.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under “Related substances”, with the following modifications:

Use as the mobile phase for isocratic elution the initial composition of the mixture of mobile phases A and B, adjusted where applicable.

Prepare the following solutions immediately before use in mobile phase. For solution (1) dissolve about 30 mg of the test substance, accurately weighed, and dilute to 50.0 mL. For solution (2) dissolve 30.0 mg of amoxicillin trihydrate RS and dilute to 50.0 mL.

Inject alternately 50 μL each of solution (1) and (2) and record the chromatograms.

Measure the areas of the peaks corresponding to amoxicillin obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of amoxicillin (C\(_{16}\)H\(_{19}\)N\(_3\)O\(_5\)S), using the declared content of amoxicillin (C\(_{16}\)H\(_{19}\)N\(_3\)O\(_5\)S) in amoxicillin trihydrate RS.

**Impurities**

A. (2S,5R,6R)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillinic acid),

B. (2S,5R,6R)-6-[[2S]-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (1-amoxicillin),
Amoxicillin trihydrate (Ph. Int.)

C. (4S)-2-[5-(4-hydroxyphenyl)-3,6-dioxopiperazin-2-yl]-5,5-dimethylthiazolidine-4-carboxylic acid (amoxicillin diketopiperazines),

D. (4S)-2-[[[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]carboxymethyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of amoxicillin),

and epimer at C*.

E. (2RS,4S)-2-[[[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penilloic acids of amoxicillin),

F. 3-(4-hydroxyphenyl)pyrazin-2-ol,
G. $(2S,5R,6R)-6-[(2R)-2-[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (d-(4-hydroxyphenyl)glycylamoxicillin),

H. $(2R)-2-[(2,2-dimethylpropanoyl)amino]-2-(4-hydroxyphenyl)acetic acid,

I. $(2R)-2$-amino-2-(4-hydroxyphenyl)acetic acid,

J. co-oligomers of amoxicillin and of penicilloic acids of amoxicillin,
K. oligomers of penicilloic acids of amoxicillin,


**Reagents to be added or to be revised**

Silica gel R3

Silica gel H

*Description.* A white, homogeneous powder.

*Particle size.* 10–40 μm.

It may or may not be silanized.

***
This is a draft proposal of a revised monograph for *The International Pharmacopoeia* (Working document QAS/16.681, February 2018). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

**[Note from the Secretariat. It is proposed to include the monograph on Clavulanate potassium in The International Pharmacopoeia. The monograph is based on laboratory investigations and on information found in the Chinese Pharmacopoeia, the European Pharmacopoeia and the United States Pharmacopoeia. Comments are in particular sought regarding the nature of the impurities listed on the transparency list, i.e. whether they are synthesis-related impurities, degradation products or both.]**

**Molecular formula.** \(\text{C}_8\text{H}_8\text{KNO}_5\).

**Relative molecular mass.** 237.3.

**Graphic formula**

![Graphic formula of Clavulanate potassium](image)

**Chemical name.** Potassium \((2R,3Z,5R)-3-(2\text{-hydroxyethylidene})-7\text{-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate, CAS Reg. No.61177-45-5.}

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

**Solubility.** Freely soluble in water R, slightly soluble in ethanol (~710 g/L) TS, very slightly soluble in acetone R.

**Category.** \(\beta\)-Lactamase inhibitor.

**Storage.** Potassium clavulanate should be kept in tightly closed containers, protected from light, at a temperature of 2°C to 8°C.

**Additional information.** Potassium clavulanate is hygroscopic.

**Requirements**

**Definition.** Potassium clavulanate contains not less than 96.5% and not more than 102.0% of \(\text{C}_8\text{H}_8\text{KNO}_5\), calculated with reference to the anhydrous substance.

**Manufacture.** The method of production is validated to demonstrate that the substance, if tested, would comply with the limit of not more than 0.01% for clavam-2-carboxylate using a suitable method.
**Identity tests**

Either tests A and D or 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 is concordant with the reference spectrum of potassium clavulanate.

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

C. [Note from the Secretariat. It is intended to add a TLC test specific for clavulanic acid and amoxicillin.]

D. Ignite a small quantity, dissolve the residue in water and filter. Add 2 mL of sodium hydroxide (~80 g/L) TS to the filtrate. It yields the reaction described under 2.1 General identification tests as characteristic of potassium.

**Solution S.** Dissolve 0.400 g of the test substance in carbon-dioxide-free water R and dilute to 20.0 mL with the same solvent.

**pH value (1.13).** Dilute 5 mL of solution S to 10 mL with carbon dioxide-free water R; the value lies between 5.5 to 8.0.

**Specific optical rotation (1.4).** Use solution S; $[\alpha]_D^{20} = +53$ to $+63$ with reference to the anhydrous substance.

**Polymeric impurities and other impurities absorbing at 278 nm**

Prepare fresh solutions and perform the test without delay.

Dissolve 50.0 mg of the test substance in phosphate buffer, pH 7.0 (0.1 mol/L) TS and dilute to 50.0 mL with the same buffer solution. Measure the absorbance immediately. The absorbance (1.6) of the solution determined at 278 nm is not greater than 0.40.

**Water.** Determine as described under 2.8 Determination of water by the Karl Fischer method, method A, using about 0.50 g of the substance; the water content is not more than 5 mg/g.

**Related substances.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (10 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).\(^1\)

Prepare the following phosphate buffer, pH 4.0. Dissolve 7.8 g of sodium dihydrogen phosphate R in about 800 mL of water R, adjust to pH 4.0 with phosphoric acid (~105 g/L) TS and dilute to 1000.0 mL with the same solvent.

Use the following conditions for gradient elution:

- **mobile phase A:** phosphate buffer, pH 4.0;
- **mobile phase B:** a mixture of equal volumes of methanol R and mobile phase A.

\(^1\) A Waters Atlantis T3 column was found suitable.
Operate with a flow rate of 1 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 230 nm. Maintain the column temperature at 40°C.

Prepare the following solutions immediately before use in mobile phase A. For solution (1) dissolve about 25 mg of the test substance and dilute to 25.0 mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3) dissolve 10 mg of lithium clavulanate R and 10 mg of amoxicillin trihydrate R and dilute to 100 mL.

Inject 20 µL of solution (3). The test is not valid unless in the chromatogram obtained the resolution between the peaks due to clavulanate (retention time about 3 minutes) and the peak due to amoxicillin (with a relative retention of about [value to be determined]) is at least 13.

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

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to clavulanate (retention time about 3 minutes): impurity E about 2.3; impurity G about 3.6.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to either impurity E or impurity G is not greater than the area of the peak due to clavulanic acid in the chromatogram obtained with solution (2) (1.0%);
- the area of any other impurity peak is not greater than 0.2 times the area of the peak due to clavulanic acid in the chromatogram obtained with solution (2) (0.2%);
- the sum of the areas of all impurity peaks is not greater than 2 times the area of the peak due to clavulanic acid in the chromatogram obtained with solution (2) (2.0%). Disregard any peak with an area less than 0.05 times the area of the peak due to clavulanic acid in the chromatogram obtained with solution (2) (0.05%).

**Aliphatic amines.** The method can be used to determine the following aliphatic amines: 1,1-dimethylethylamine (impurity H); \(N,N,N',N'\)-tetramethylethylene diamine (impurity J); 1,1,3,3-tetramethyl butylamine (impurity K); \(N,N'\)-diisopropylethane-1,2-diamine (impurity L); 2,2’-oxybis(\(N,N'\))-dimethylethylamine (impurity M).

Carry out the test as described under **1.14.5 Gas chromatography.** Use a fused-silica capillary column, 50 m long and 0.53 mm in internal diameter, coated with poly(dimethyl)(diphenyl) siloxane R (film thickness: 5 µm).

As an internal standard use a solution containing 0.5 µL of 3-methylpentane-2-one R per mL of water R. For solution (1) transfer 1.00 g of the test substance to a centrifuge tube. Add 5.0 mL of the internal standard solution, 5.0 mL of sodium hydroxide (~8.5 g/L) TS, 10.0 mL
Clavulanate potassium (Ph. Int.)

of water R, 5.0 mL of 2-methylpropanol R and 5 g of sodium chloride R. Shake vigorously for 1 minute. Centrifuge to separate the layers and use the upper layer. For solution (2) dissolve 80.0 mg of each of the following amines: 1,1-dimethylethylamine R; tetramethylethylene diamine R; 1,1,3,3-tetramethylbutylamine R; N,N’-diisopropylethylenediamine R and 2,2’-oxybis(N,N-dimethylethylamine) R in hydrochloric acid (~70 g/L) TS and dilute to 200.0 mL with the same acid. Transfer 5.0 mL of this solution into a centrifuge tube. Add 5.0 mL of the internal standard solution, 10.0 mL of sodium hydroxide (~8.5 g/L) TS, 5.0 mL of 2-methylpropanol R and 5 g of sodium chloride R. Shake vigorously for 1 minute. Centrifuge to separate the layers and use the upper layer.

As a detector use a flame ionization detector.

Use nitrogen R as the carrier gas at an appropriate pressure and a split ratio 1:10 with a flow rate of about 6 mL/min.

Maintain the temperature of the column at 35°C for 7 minutes, then raise the temperature at a rate of 30°C per minutes to 150°C and maintain for 15 minutes. Keep the temperature of the injection port at 200°C and that of the flame ionization detector at 250°C.

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

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to 3-methylpentane-2-one (internal standard, retention time about 11.4 minutes): impurity H about 0.55; impurity J about 1.07; impurity K about 1.13; impurity L about 1.33; impurity M about 1.57.

Measure the peak responses of the aliphatic amines and of the internal standard. Calculate the percentage content of each impurity using the ratios of the responses of the each aliphatic amine to the responses of the internal standard. Use the ratios of the peak responses of the corresponding reagents as a reference. The sum of the percentage contents of all aliphatic amines is less than 0.2%.

2-Ethylhexanoic acid. Carry out the test as described under 1.14.5 Gas chromatography.

Use a fused-silica capillary column 10 m long and 0.53 mm in internal diameter coated with macrogol 20000 2-nitrotetraphthalate R (film thickness: 1.0 µm).

As an internal standard use a solution containing 1.0 mg 3-cyclohexylpropionic acid R per mL of cyclohexane R. For solution (1) transfer 1.00 g of the test substance to a centrifuge tube. Add 4.0 mL of a 33% (V/V) solution of hydrochloric acid R. Shake vigorously for 1 minute with 1.0 mL of the internal standard solution. Allow the phases to separate (if necessary, centrifuge for a better separation). Use the upper layer. For solution (2) dissolve 75.0 mg of 2-ethylhexanoic acid R in the internal standard solution and dilute to 50.0 mL with the same solution. To 1.0 mL of the solution add 4.0 mL of a 33% (V/V) solution of hydrochloric acid R. Shake vigorously for 1 minute. Allow the phases to separate (if necessary, centrifuge for a better separation). Use the upper layer.

As a detector use a flame ionization detector.

Use nitrogen as the carrier gas at an appropriate pressure with a flow rate of about 6 mL/minute.
Maintain the temperature of the column at 40°C for 2 minutes, then raise the temperature at a rate of 30°C per minutes to 200°C and maintain for 3 minutes. Keep the temperature of the injection port at 200°C and that of the flame ionization detector at 300°C.

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

The test is not valid unless the resolution between the peaks due to 2-ethylhexanoic acid (first peak) and due to the internal standard is at least 2.0.

Measure the peak responses of 2-ethylhexanoic acid and of the internal standard. Calculate the percentage content of 2-ethylhexanoic acid in the test substance using the ratios of the responses of 2-ethylhexanoic acid to the responses of the internal standard; the content is not more than 0.8%.

**Assay.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (40 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecysilyl groups (10 µm).²

Prepare the following phosphate buffer, pH 4.0. Dissolve 15 g of sodium dihydrogen phosphate R in about 800 mL of water R, adjust to pH 4.0 with phosphoric acid (~105 g/L) TS and dilute to 1000.0 mL with the same solvent.

As the mobile phase use a mixture of 5 volumes of methanol R and 95 volumes of phosphate buffer, pH 4.0.

Operate with a flow rate of 1 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 230 nm.

Prepare the following acetate buffer, pH 6.0. Dissolve 4.1 g of sodium acetate R in about 800 mL of water R, adjust to pH 6.0 with glacial acetic acid R and dilute to 1000.0 mL with the same solvent.

Prepare the following solutions immediately before use, using acetate buffer, pH 6.0 as the solvent. For solution (1) dissolve 50.0 mg of the test substance and dilute to 50.0 mL. For solution (2) dissolve 50.0 mg of lithium clavulanate RS and dilute to 50.0 mL. For solution (3) dissolve 10 mg of amoxicillin trihydrate R in 10 mL of solution (2).

Inject 10 µL of solution (3). The assay is not valid unless the resolution between the peaks due to clavulanate (retention time about 5 minutes) and the peak due to amoxicillin (with a relative retention of about [value to be determined]) is at least 3.5.

Measure the areas of the peaks corresponding to clavulanate obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of $C_8H_8KNO_5$, using the declared content of clavulanic acid ($C_8H_9NO_5$) in lithium clavulanate RS. 1 mg of clavulanic acid ($C_8H_9NO_5$) is equivalent to 1.191 mg of potassium clavulanate $C_8H_8KNO_5$.

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² A Zorbax eclipse XDB-C18 column was found suitable.
Clavulanate potassium (Ph. Int.)

**Impurities**

A. 2,2’-(pyrazine-2,5-diyl)diethanol

B. 3-[3,6-bis(2-hydroxyethyl)pyrazin-2-yl]propanoic acid

C. 2,2’-(3-ethylpyrazine-2,5-diyl)diethanol

D. 4-(2-hydroxyethyl)-1H-pyrrole-3-carboxylic acid

E. (2R,4R,5Z)-2-(carboxymethyl)-5-(2-hydroxyethylidene)-3-[[2R,3Z,5R]-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]oxazolidine-4-carboxylic acid

F. 4-[[4-(2-hydroxyethyl)-1H-pyrrol-3-yl]carbonyl]oxy]methyl]-1H-pyrrole-3-carboxylic acid
G. 4-[[1S]-1-carboxy-2-(4-hydroxyphenyl)ethyl]amino]-4-oxobutanoic acid (N-(hydrogensuccinyl)tyrosine)

H. 2-methylpropan-2-amine (2-amino-2-methylpropane, tert-butylamine, 1,1-dimethylethylamine)

J. N,N,N',N'-tetramethylethane-1,2-diamine (1,2-bis(dimethylamino)ethane, N,N,N',N'-tetramethylethlenediamine)

K. 2,4,4-trimethylpentane-2-amine (2-amino-2,4,4-trimethylpentane, 1,1,3,3-tetramethylbutylamine)

L. N,N'-diisopropylethane-1,2-diamine (N,N'-bis(1-methylethyl)ethane-1,2-diamine)

M. 2,2'-oxybis(N,N-dimethylethanamine), bis[2-(dimethylamino)ethyl] ether, N,N,N',N'-tetramethyl(oxydiethylene)diamine

Reagents to be established

Amoxicillin trihydrate R
Amoxicillin trihydrate of a suitable quality should be used.

3-Cyclohexylpropionic acid R
C₉H₁₆O₂
Molecular weight. 156.2.
Description. Clear liquid.
Relative density $d_{20}^0$. About 0.998.
Boiling point. About 130°C.

N,N'-Diisopropylethlenediamine R
$C_8H_{20}N_2$
Molecular weight. 144.3.
Other name. N,N'-Bis(1-methylethyl)-1,2-ethanediamine.
Description. Colourless or yellowish, hygroscopic liquid, corrosive, flammable.
Relative density $d_{20}^0$. About 0.798.
Boiling point. About 170°C.

1,1-Dimethylethylamine R
$C_4H_{11}N$
Molecular weight. 73.1.
Other names. 2-Amino-2-methylpropane, tert-Butylamine.
Description. Liquid, miscible with ethanol (~710 g/L) TS.
Relative density $d_{20}^0$. About 0.694.
Boiling point. About 46°C.

2-Ethylhexanoic acid R
$C_8H_{16}O_2$
Molecular weight. 144.2.
Description. Colourless liquid.
Relative density $d_{20}^0$. About 0.91.
Related substances. Carry out the test as described under 1.14.5 Gas chromatography using the conditions given in the test for 2-ethylhexanoic acid in the monograph on Potassium clavulanate. Prepare the following solution: suspend 0.2 g of 2-ethylhexanoic acid in 5 mL of water R, add 3 mL of 33% (V/V) solution of hydrochloric acid R and 5 mL of hexane R, shake for 1 minute, allow the layers to separate and use the upper layer. Inject 1 µL of this solution. The sum of the area of any peaks, other than the principal peak and the peak due to the solvent, is not greater than 2.5% of the area of the principal peak.

Lithium clavulanate R
Lithium clavulanate of a suitable quality should be used.

Macrogol 20000 R
Description. White or almost white solid with a waxy or paraffin-like appearance.
Solubility. Very soluble in water, soluble in methylene chloride, practically insoluble in alcohol, in fatty oils and in mineral oils.

Macrogol 20000 2-nitrotetraphthalate R
Macrogol 20000 R modified by treating with 2-nitrotetraphthalate acid.
Description. A hard, white or almost white, waxy solid.
Solubility. Soluble in acetone R.

3-Methylpentane-2-one R
$C_6H_{12}O$
Molecular weight. 100.2.
Description. Colourless, flammable liquid.
Relative density \( \rho_{20} \). About 0.815.
Boiling point. About 118°C.

2-Methylpropanol R
\( \text{C}_4\text{H}_{10}\text{O} \)
Molecular weight. 74.1.
Other names. Isobutyl alcohol, 2-Methylpropan-1-ol.
Description Clear colourless liquid.
Solubility. Soluble in water, miscible with ethanol (~710 g/L) TS.
Relative density \( \rho_{20} \). About 0.80.
Boiling point. About 107°C.

2,2'-Oxybis(N,N-dimethylethylamine) R
\( \text{C}_8\text{H}_{20}\text{N}_2\text{O} \)
Molecular weight. 160.3.
Other name. Bis(2-dimethylaminoethyl) ether.
Description. Colourless, corrosive liquid.
Relative density \( \rho_{20} \). About 0.85.

Phosphate buffer, pH 7.0 (0.1 mol/L) TS
Procedure. Dissolve 1.361 g of potassium dihydrogen phosphate R in 100.0 mL of water. Adjust the pH using a 14.20 g/L solution of anhydrous disodium hydrogen phosphate R.

Poly(dimethyl)(diphenyl)siloxane R
Stationary phase for gas chromatography. Contains 95% of methyl groups and 5% of phenyl groups.

Sodium hydroxide (~8.5 g/L) TS
A solution of sodium hydroxide R containing about 8.5 g/L of NaOH.

1,1,3,3-Tetramethylbutylamine R
\( \text{C}_8\text{H}_{19}\text{N} \)
Molecular weight. 129.3.
Other name. 2-Amino-2,4,4-trimethylpentane.
Description. Clear, colourless liquid.
Relative density \( \rho_{20} \). About 0.805.
Boiling point. About 140°C.

Tetramethylethylenediamine R
\( \text{C}_6\text{H}_{16}\text{N}_2 \)
Molecular weight. 116.2.
Other name. N,N,N',N'-Tetramethylethylenediamine.
Description. Colourless liquid, miscible with water and with ethanol (~710 g/L) TS.
Relative density \( \rho_{20} \). About 0.78.
Boiling point. About 121°C.

***
Amoxicillin and clavulanic acid tablets
(Amoxicillini et acidi clavulanici compressi)

This is a draft proposal of a monograph for The International Pharmacopoeia
(Working document QAS/16.660, February 2018). The working document with
line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

[Note from the Secretariat. It is proposed to include the monograph on Amoxicillin and clavulanic acid tablets in The International Pharmacopoeia. The monograph is based on laboratory investigations and on information found in the British Pharmacopoeia, the Chinese Pharmacopoeia, the European Pharmacopoeia and the United States Pharmacopeia.]

Category. Antibacterial, β-Lactamase inhibitor.

Storage. Amoxicillin and clavulanic acid tablets should be kept in a tightly closed container and protected from light.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML): 500 mg amoxicillin (as trihydrate) and 125 mg clavulanic acid (as potassium salt). Strength in the current EML for Children: 500 mg amoxicillin (as trihydrate) and 125 mg clavulanic acid (as potassium salt).

Labelling. The designation on the container should state that the active ingredients are amoxicillin trihydrate and clavulanate potassium and that the quantities should be indicated in terms of equivalent amounts of amoxicillin and clavulanic acid.

Requirements
Comply with the monograph for Tablets.

Definition. Amoxicillin and clavulanic acid tablets contain amoxicillin trihydrate and clavulanate potassium. They contain not less than 90.0% and not more than 120.0% of the amounts of amoxicillin (C$_{16}$H$_{19}$N$_3$O$_5$S) and clavulanic acid (C$_8$H$_9$NO$_5$) stated on the label.

Identity test
Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”. The retention times of the two principal peaks in the chromatogram obtained with solution (1) correspond to the retention times of the peaks due to amoxicillin and clavulanic acid in the chromatogram obtained with solution (2).

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using a quantity of the powdered tablets; the water content is not more than 100 mg/g. The limit is applicable for tablets 500 mg amoxicillin (as trihydrate).

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 water R 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, dilute with water if necessary, to obtain a solution containing the equivalent of about 0.25 mg of amoxicillin per mL (solution (1)). For solution (2) dissolve a suitable amount of amoxicillin trihydrate RS and lithium clavulanate RS in a suitable volume of water R to obtain a solution containing about 0.25 mg of amoxicillin and about 0.0625 mg of clavulanic acid per mL.

Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions as described under “Assay”.

For each of the tablets tested, calculate the total amount of amoxicillin \((\text{C}_{16}\text{H}_{19}\text{N}_{3}\text{O}_{5}\text{S})\) and clavulanic acid \((\text{C}_{8}\text{H}_{9}\text{N}_{5}\text{O}_{5})\) in the medium using the declared content of amoxicillin \((\text{C}_{16}\text{H}_{19}\text{N}_{3}\text{O}_{5}\text{S})\) in amoxicillin trihydrate RS and the declared content of clavulanic acid \((\text{C}_{8}\text{H}_{9}\text{N}_{5}\text{O}_{5})\) in lithium clavulanate RS.

The amount of amoxicillin and clavulanic acid in solution for each tablet is not less than 75% \((Q)\) of the amount declared on the label.

**Clavulanate polymer and other fluorescent impurities.** Carry out the test as described under 1.9 Fluorescence spectrophotometry.

Prepare the following buffer solution. Dissolve 15.6 g of sodium dihydrogen phosphate R in 800 mL of water R, adjust the pH to 5.0 using sodium hydroxide (~40 g/L) TS and add sufficient water R to produce 1000 mL.

Prepare the following solutions freshly. For solution (1) add to a quantity of the powdered tablets, containing the equivalent of 0.1 g of clavulanic acid, 50 mL of the buffer solution. Stir the sample until it is evenly dispersed and add sufficient buffer solution to produce 100.0 mL. Shake the solution vigorously for 1 minute, shake mechanically for 5 minutes, sonicate for 5 minutes and filter. For solution (2) prepare a solution containing 0.42 µg per mL of quinine sulfate R in sulfuric acid (~50 g/L) TS.

Measure the fluorescence of the solutions (1) and (2) with an excitation wavelength of 360 nm and an emission wavelength of 440 nm, using the phosphate buffer solution in the reference cell. The fluorescence obtained with solution (1) is not more intense than that obtained with solution (2) (5% w/w, calculated with respect to the content of clavulanic acid). [Note: The fluorescence of quinine sulfate is 118 times more intense than that of an equivalent concentration of clavulanate polymer.]

**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).1

Prepare the following buffer solution, pH 5.0: adjust the pH of 250 mL of potassium dihydrogen phosphate (27.2 g/L) TS to 5.0 with sodium hydroxide (~80 g/L) TS and dilute to 1000 mL with water R.

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1 Shim-pack CL-ODS \(\text{C}_{18}\) has been found suitable.
Amoxicillin and clavulanic acid tablets (Ph. Int.)

Use the following conditions for gradient elution:

- mobile phase A: mix 10 volumes of acetonitrile R with 990 volumes of the buffer solution;
- mobile phase B: mix 200 volumes of acetonitrile R with 800 volumes of the buffer solution.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – tr</td>
<td>92</td>
<td>8</td>
<td>Isocratic</td>
</tr>
<tr>
<td>tr – (tr + 25)</td>
<td>92 to 0</td>
<td>8 to 100</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>(tr + 25) – (tr + 40)</td>
<td>0</td>
<td>100</td>
<td>Isocratic</td>
</tr>
<tr>
<td>(tr + 40) – (tr + 41)</td>
<td>92</td>
<td>8</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>(tr + 41) – (tr + 55)</td>
<td>92</td>
<td>8</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

tr = retention time of amoxicillin determined with solution (1).

Prepare the following solutions immediately before use. For solution (1) transfer a quantity of the powdered tablets containing the equivalent of about 30 mg of amoxicillin into a 20 mL volumetric flask, add 15 mL of mobile phase A and sonicate for 20 minutes with occasional shaking. Allow to cool to room temperature, make up to volume with mobile phase A and filter. For solution (2) dilute 1 volume of solution (1) to 100 volumes with mobile phase A. For solution (3) use a solution containing 4 μg of cefadroxil R and 30 μg of amoxicillin RS per mL mobile phase A. For solution (4) use a solution containing 0.75 mg of lithium clavulanate RS per mL mobile phase A. For solution (5) add 1.0 mL of water R to 0.20 g of amoxicillin trihydrate R. Shake and add dropwise sodium hydroxide (~80 g/L) TS to obtain a solution. The pH of the solution is about 8.5. Store the solution at room temperature for 4 h. Dilute 0.5 mL of this solution to 50.0 mL with mobile phase A.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Inject 50 μL of solution (3) with isocratic elution at the initial mobile phase composition. The test is not valid unless the resolution factor between the peaks due to amoxicillin and cefadroxil is at least 2.0.

Inject alternately 50 μL each of solution (4) and (5). Use the chromatogram obtained with solution (4) to identify the peak corresponding to clavulanic acid. Use the chromatogram obtained with solution (5) to identify the peaks corresponding to amoxicillin dimer (impurity J; n = 1) and amoxicillin trimer (impurity J; n = 2). The following impurities and substances are eluted at the relative retention with reference to amoxicillin (retention time about 10 minutes): clavulanic acid about 0.3; amoxicillin dimer (impurity J; n = 1) about 4.1; amoxicillin trimer (impurity J; n = 2) about 4.5.

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

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to amoxicillin dimer (impurity J; n = 1) is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2%).
the area of any other impurity peak is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Assay. 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).¹

As the mobile phase use a mixture of 5 volumes of methanol R and 95 volumes of sodium dihydrogen phosphate (~7.8 g/L) TS, adjusted to pH 4.4 with phosphoric acid (~1440 g/L) TS.

Operate with a flow rate of 2.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 220 nm.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing the equivalent of about 0.25 g of amoxicillin, accurately weighed, into a 500 mL volumetric flask, add 400 mL of water R and shake for 10 minutes. Make up to volume with water R and filter. For solution (2) use 0.5 mg of amoxicillin RS and 0.2 mg of lithium clavulanate RS per mL water R.

Inject alternately 20 μL of solution (1) and (2). The assay is not valid unless the resolution factor between the peaks due to amoxicillin and clavulanic acid is at least 3.5 and the symmetry factor of the peak due to clavulanic acid in the chromatogram obtained with solution (2) is less than 1.5.

Measure the areas of the peak responding to amoxicillin and clavulanic acid and calculate the content of amoxicillin (C₁₆H₁₉N₃O₅S) and clavulanic acid (C₈H₉NO₅) in the tablets using the declared content of amoxicillin (C₁₆H₁₉N₃O₅S) in amoxicillin trihydrate RS and the declared content of clavulanic acid (C₈H₉NO₅) in lithium clavulanate RS.

Impurities

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

Reagents and test solutions to be established

Phosphoric acid (~7.8 g/L) TS

Procedure. Dilute 9.2 g of phosphoric acid (~1440 g/L) TS with sufficient water to produce 1000 mL.

Sulfuric acid (~50 g/L) TS

Procedure. Mix 500 mL of sulfuric acid (~100 g/L) TS with sufficient water to produce 1000 mL.

Quinine sulfate R

Quinine sulfate of a suitable quality should be used.

Cefadroxil R

Cefadroxil of a suitable quality should be used.

***
Dissolution test for solid oral dosage forms

This is a draft proposal of a revised monograph for The International Pharmacopoeia (Working document QAS/18.756, February 2018). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

[Note from the Secretariat. Following the publication of the document Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability it is proposed to add an acetate buffer pH 4.5 to chapter 5.5 Dissolution test for solid oral dosage forms to assist the guidelines recommendation that pharmacopoeial buffers should be used to determine the in vitro dissolution characteristics of multisource products. It is further proposed to revise the requirements for the qualification of dissolution testers by introducing the concept of an “enhanced mechanical calibration”. The text prescribes that the pH of buffers used as dissolution media has to be adjusted to within 0.05 units of the specified value. Advice is sought whether this adjustment has to be made at the temperature at which the dissolution test is usually performed, i.e. 37 ± 0.5°C (see line 144 of the working document available at www.who.int/medicines/areas/quality_safety/quality_assurance/projects). In the online document, changes from the current chapter are indicated in the text by insert or delete.]

5.5 Dissolution test for solid oral dosage forms

This text is based on the internationally-harmonized texts developed by the Pharmacopoeial Discussion Group (PDG). It has been developed in line with the style and requirements used in The International Pharmacopoeia. The additional section on monographs of The International Pharmacopoeia is not part of the PDG text.

For further guidance, see also the chapter Dissolution testing of tablets and capsules in the Supplementary Information section.

This test determines the amount of active ingredient(s) released from a solid oral dosage form, such as a tablet or a capsule, under controlled conditions using a known volume of dissolution medium within a predetermined length of time.

Basket apparatus. The assembly consists of the following: a vessel, which may be covered, made of glass or other inert, transparent material, which should not sorb, react or interfere with the dosage form, the active ingredient or the dissolution medium; a motor; a drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water-bath of any convenient size or heated by a suitable device such as a heating jacket to maintain the temperature inside the vessel at 37 ± 0.5°C during the test and to keep the dissolution medium in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the preparation and stirring element during the test is preferable. The vessel is cylindrical with a hemispherical bottom and a capacity of 1 litre. Its height is 160–210 mm and its inside diameter is 98–106 mm. Its sides are flanged at the top. A fitted cover may be used to retard evaporation. If a cover is used it provides sufficient openings to allow ready insertion of the thermometer.
and withdrawal of samples. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble that could affect the results. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at a specified rate within ± 4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure 1. A basket having a gold coating of about 2.5 µm (0.0001 inch) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the bottom of the basket is maintained at 25 ± 2 mm during the test.

Figure 1. Basket stirring element.
Dimensions in millimetres

1. Screen with welded seam: 0.22–0.31 mm wire diameter with wire opening of 0.36–0.44 mm. After welding the screen may be slightly altered.
2. Maximum allowable runout at “A” is 1.0 mm when the part is rotated on centre line axis with basket mounted.
A and B dimensions do not vary more than 0.5 mm when part is rotated on centre line axis. Tolerances are ± 1.0 mm unless otherwise stated.

Figure 2. **Paddle stirring element.**
Dimensions in millimetres

**Paddle apparatus.** Use the assembly from the basket apparatus except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm from the vertical axis of the vessel at any point and rotates smoothly without significant wobble that could affect the results. The vertical centre line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom
Dissolution test for solid oral dosage forms (Ph. Int.)

of the shaft. The paddle conforms to the specifications shown in Figure 2. The distance of 25 ± 2 mm between the bottom of the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during the test. The paddle blade and shaft may be coated with a suitable coating so as to make them inert. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of non-reactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float. An alternative sinker device is shown in Figure 3. Other validated sinker devices may be used.

![Figure 3. Alternative sinker. Dimensions in millimeters.](image)

**Recommended procedure**

**Conventional-release (or immediate-release) dosage forms**

*Procedure.* Place the stated volume of the dissolution medium (± 1%) in the vessel of the specified apparatus. Assemble the apparatus, equilibrate the dissolution medium to 37 ± 0.5°C and remove the thermometer. The test may also be carried out with the thermometer in place, provided it is shown that results equivalent to those obtained without the thermometer are obtained. Place one dosage unit in the apparatus taking care to exclude air bubbles from the surface of the dosage unit. Operate the apparatus at the specified rate. Within the time interval specified, or at each of the times stated, withdraw a sample from a zone midway between the surface of the dissolution medium and the top of the rotating basket or blade not less than 1 cm from the vessel wall. Where multiple sampling times are specified replace the samples withdrawn for analysis with equal volumes of fresh dissolution medium at 37°C or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test and verify the temperature (37 ± 0.5°C) of the medium at suitable times. Perform the analysis as directed in the individual monograph using a suitable assay method. Test samples are filtered immediately upon sampling using in-line filtration unless filtration is demonstrated to be unnecessary. Use an inert filter that does not cause adsorption of the active substance or contain extractable
Dissolution test for solid oral dosage forms (Ph. Int.)

substances that would interfere with the analysis. Centrifugation is not recommended unless validated for the specific test. The test is to be conducted with six dosage form units in parallel.

If automated equipment is used for sampling or the apparatus is otherwise modified verification is necessary that the modified apparatus will produce results equivalent to those obtained with the apparatus described in this chapter.

**Dissolution medium.** A suitable dissolution medium is used. The volume specified refers to measurements made between 20°C and 25°C. If the dissolution medium is a buffered solution allow the medium to equilibrate to a temperature of 37 ± 0.5°C and adjust the solution so that its pH is within 0.05 units of the specified pH. Dissolved gases can cause bubbles to form which may change the results of the test. In such cases dissolved gases must be removed prior to testing.¹

**Time.** Where a single time specification is given the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. Samples are to be withdrawn only at the stated times, within a tolerance of ± 2%.

Determine the quantity of active ingredient dissolved at the specified time(s) indicated in the individual monograph. The result should be expressed as a percentage of the content stated on the label of the dosage form.

**Sustained-release solid dosage forms**

**Procedure.** Proceed as described for conventional-release dosage forms.

**Dissolution medium.** Proceed as described for conventional-release dosage forms.

**Time.** The test-time points, generally three, are expressed in hours.

**Delayed-release, solid dosage forms**

**Procedure.** Use method A or B.

Method A

- **Acid stage.** Place 750 mL hydrochloric acid (0.1 mol/L) VS in the vessel and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°C. Place one dosage unit in the apparatus, cover the vessel and operate the apparatus at the specified rate. After 2 hours of operation in hydrochloric acid (0.1 mol/L) VS withdraw a sample of the fluid and proceed immediately as directed under buffer stage. Perform an analysis of the sample using a suitable assay method.

- **Buffer stage.** Complete the operations of adding and adjusting the pH within 5 minutes. With the apparatus operating at the rate specified add to the fluid in the vessel 250 mL of a 0.2 M solution of trisodium orthophosphate R that has been equilibrated to 37 ± 0.5°C. Adjust, if necessary, with hydrochloric acid (~70 g/L) TS or sodium hydroxide (~80 g/L)

¹ One appropriate method of deaeration is as follows: heat the medium, while stirring gently, to about 41°C, immediately filter under vacuum using a filter having a pore size of 0.45 µm or less, with vigorous stirring and continue stirring under vacuum for at least 5 minutes, preferably 15 minutes, until no more bubbles are observed. Other validated deaeration techniques for removal of dissolved gases may be used.
TS to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes or for the specified time. At the end of the time period withdraw a sample of the fluid and perform the analysis using a suitable assay method.

Method B

- **Acid Stage.** Place 1000 mL of hydrochloric acid (0.1 mol/L) VS in the vessel and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°C. Place one dosage unit in the apparatus, cover the vessel and operate the apparatus at the specified rate. After 2 hours of operation in hydrochloric acid (0.1 mol/L) VS withdraw a sample of the fluid and proceed immediately as directed under buffer stage. Perform an analysis of the sample using a suitable assay method.

- **Buffer stage.** For this stage of the procedure use buffer that has previously been equilibrated to a temperature of 37 ± 0.5°C. Drain the acid from the vessel and add 1000 mL of pH 6.8 phosphate buffer, prepared by mixing three volumes of hydrochloric acid (0.1 mol/L) VS with one volume of a 0.20 M solution of trisodium orthophosphate R and adjusting, if necessary, with hydrochloric acid (~70 g/L) TS or sodium hydroxide (~80 g/L) TS to a pH of 6.8 ± 0.05. This may also be accomplished by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer and transferring the dosage unit to the vessel containing the buffer. Continue to operate the apparatus for 45 minutes or for the specified time. At the end of the time period withdraw a sample of the fluid and perform the analysis using a suitable assay method.

**Time.** All test times stated are to be observed within a tolerance of ± 2%, unless otherwise specified.

**Acceptance criteria**

**Conventional-release (or immediate-release) dosage forms**

Unless otherwise specified in the individual monograph the requirements are met if the quantities of active ingredient(s) dissolved from the dosage forms tested conform to Table 1. Continue testing through the three levels unless the results conform at either $S_1$ or $S_2$. The quantity, $Q$, is the specified amount of dissolved active ingredient expressed as a percentage of the labelled content; the 5%, 15% and 25% values in the acceptance table are percentages of the labelled content so that these values and $Q$ are in the same terms.

**Table 1**

<table>
<thead>
<tr>
<th>Level</th>
<th>Samples tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_1$</td>
<td>6</td>
<td>Each value is not less than $Q + 5%$</td>
</tr>
<tr>
<td>$S_2$</td>
<td>6</td>
<td>Average value of the 12 dosage units ($S_1 + S_2$) is equal to or greater than $Q$ and no unit is less than $Q - 15%$</td>
</tr>
<tr>
<td>$S_3$</td>
<td>12</td>
<td>Average value of 24 dosage units ($S_1 + S_2 + S_3$) is equal to or greater than $Q$; not more than 2 units are less than $Q - 15%$; no unit is less than $Q - 25%$.</td>
</tr>
</tbody>
</table>
Sustained release dosage forms

Unless otherwise specified in the individual monograph the requirements are met if the quantities of active ingredient(s) dissolved from the dosage forms tested conform to Table 2. Continue testing through the three levels unless the results conform at either L₁ or L₂. Limits on the amounts of active ingredient(s) dissolved are expressed in terms of the labelled content. The limits embrace each value of Qᵢ, the amount dissolved at each specified fractional dosing interval. Where more than one range is specified the acceptance criteria apply individually to each range.

Table 2

<table>
<thead>
<tr>
<th>Level</th>
<th>Samples tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>L₁</td>
<td>6</td>
<td>No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time</td>
</tr>
<tr>
<td>L₂</td>
<td>6</td>
<td>The average value of the 12 dosage units (L₁ + L₂) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of the labelled content outside each of the stated ranges; and none is more than 10% of labelled content below the stated amount at the final test time</td>
</tr>
<tr>
<td>L₃</td>
<td>12</td>
<td>The average value of the 24 dosage units (L₁ + L₂ + L₃) lies within the stated ranges and is not less than the stated amount at the final test time; not more than 2 of the 24 dosage units are more than 10% of labelled content outside each of the stated ranges; not more than 2 of the 24 dosage units are more than 10% of labelled content below the stated amount at the final test time; and none of the 24 dosage units is more than 20% of labelled content below the stated content at the final test time; none of the units are more than 20% of labelled content outside each of the stated ranges or more than 20% of labelled content below the stated amount at the final test time</td>
</tr>
</tbody>
</table>

Delayed-release dosage forms

Acid stage. Unless otherwise stated in the individual monograph the requirements of this part of the test are met if the quantities, based on the percentage of the labelled content of active ingredient(s) dissolved from the dosage units tested conform to Table 3. Continue testing through the three levels unless the results of both acid and buffer stages conform at an earlier level.

Table 3

<table>
<thead>
<tr>
<th>Level</th>
<th>Samples tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₁</td>
<td>6</td>
<td>No individual value exceeds 10% dissolved</td>
</tr>
<tr>
<td>A₂</td>
<td>6</td>
<td>Average value of the 12 dosage units (A₁ + A₂) is not more than 10% dissolved, and no individual value is greater than 25% dissolved</td>
</tr>
<tr>
<td>A₃</td>
<td>12</td>
<td>Average value of 24 dosage units (A₁ + A₂ + A₃) is not more than 10% dissolved, and no individual value is greater than 25% dissolved.</td>
</tr>
</tbody>
</table>

Buffer stage. Unless otherwise specified in the individual monograph the requirements are met if the quantities of active ingredients dissolved from the units tested conform to Table 4. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of Q in Table 4 is the specified total amount of API dissolved in both the acid
and buffer stages, expressed as a percentage of the labelled content. The 5%, 15% and 25% values in the table are percentages of the labelled content so that these values and Q are in the same terms.

**Table 4**

<table>
<thead>
<tr>
<th>Level</th>
<th>Samples tested</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>B₁</td>
<td>6</td>
<td>No value is less than $Q + 5%$</td>
</tr>
<tr>
<td>B₂</td>
<td>6</td>
<td>Average value of the 12 dosage units ($B₁ + B₂$) is equal to or greater than $Q$, and no unit is less than $Q - 15%$</td>
</tr>
<tr>
<td>B₃</td>
<td>12</td>
<td>Average value of the 24 dosage units ($B₁ + B₂ + B₃$) is equal to or greater than $Q$; not more than 2 units are less than $Q - 15%$, and no unit is less than $Q - 25%$.</td>
</tr>
</tbody>
</table>

**Monographs of The International Pharmacopoeia**

The following additional statements apply to the individual monographs of The International Pharmacopoeia.

**Performance of dissolution test equipment**

Periodically qualify the equipment utilizing an “enhanced mechanical calibration” such as the procedure described in the international standard procedure ASTM 2503-07 or a combination of a mechanical calibration to determine conformance of the dissolution tester to the dimensions and tolerances as given above and the analysis of suitable reference tablets to verify the performance of the test assembly.

**Test conditions**

The following specifications are given in the individual monographs:

- the apparatus to be used;
- the composition and volume of the dissolution medium;
- the rotation speed of the paddle or basket;
- the preparation of the test and reference solutions;
- the time, the method and the amount for sampling of the test solution or the conditions for continuous monitoring;
- the method of analysis;
- the limits of the quantity or quantities of active pharmaceutical ingredient(s) required to dissolve within a prescribed time.

**Dissolution media**

If a buffer is added to the dissolution medium adjust its pH to within ± 0.05 units of the prescribed value.

In specific cases, and subject to approval by the relevant regional or national authority, dissolution media may contain enzymes and/or surfactants. The addition of enzymes may be considered, for example, for formulations containing gelatin in the outer layer when dissolution failures can be ascribed to the cross-linking of this excipient (e.g. hard and soft
gelatin capsules). For the testing of preparations containing poorly aqueous-soluble active substances modification of the medium may be necessary. In such circumstances a low concentration of surfactant may be prescribed.

Below are some examples of dissolution media.

• **Dissolution buffer pH 1.3, TS**
  Dissolve 2 g of sodium chloride R in 800 mL of water R, adjust the pH to 1.3 with hydrochloric acid (~70 g/L) TS and dilute to 1000 mL with water R.

• **Dissolution buffer pH 2.5, TS**
  Dissolve 2 g of sodium chloride R in 800 mL of water R, adjust the pH to 2.5 with hydrochloric acid (~70 g/L) TS and dilute to 1000 mL with water R.

• **Dissolution buffer pH 3.5, TS**
  Dissolve 7.507 g of glycine R and 5.844 g of sodium chloride R in 800 mL of water R, adjust the pH to 3.5 with hydrochloric acid (~70 g/L) TS and dilute to 1000 mL with water R.

• **Dissolution buffer pH 4.5, TS1**
  Dissolve 2.99 g of sodium acetate R in 900 mL of water R, adjust the pH to 4.5 by adding about 14 mL of acetic acid (~120 g/L) TS and dilute to 1000 mL with water R.

• **Dissolution buffer pH 4.5, TS2**
  Dissolve 6.8 g of potassium dihydrogen phosphate R in 900 mL of water R, adjust the pH to 4.5 either with hydrochloric acid (~70 g/L) TS or sodium hydroxide (~80 g/L) TS and dilute to 1000 mL with water R.

• **Dissolution buffer, pH 6.8, TS**
  Dissolve 9.075 g of potassium dihydrogen phosphate R in water R to produce 1000 mL (solution A). Dissolve 11.87 g of disodium hydrogen phosphate R in sufficient water R to produce 1000 mL (solution B). Mix 300 mL of solution A with 700 mL of solution B.

• **Gastric fluid, simulated, TS**
  Dissolve 2.0 g of sodium chloride R and 3.2 g of pepsin R in 7.0 mL of hydrochloric acid (~420 g/L) TS and sufficient water R to produce 1000 mL. This test solution has a pH of about 1.2.

• **Intestinal fluid pH 6.8, simulated, TS**
  Mix 77.0 mL of sodium hydroxide (0.2 mol/L) VS, 250.0 mL of a solution containing 6.8 g potassium dihydrogen phosphate R and 500 mL of water R. Add 10.0 g pancreatin R, mix and adjust pH to 6.8 ± 0.1. Dilute to 1000 mL with water R.

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