WHO Drug Information

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CHMP Committee for Medicinal Products for Human Use (EMA)
EMA European Medicines Agency (www.ema.europa.eu)
EU European Union
FDA U.S. Food and Drug Administration (www.fda.gov)
Health Canada Federal department responsible for health product regulation in Canada (www.hc-sc.gc.ca)
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/)
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)
WHO EMP WHO Essential medicines and health products (www.who.int/medicines/en/)
WHO PQT WHO Prequalification team (https://extranet.who.int/prequal/)

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.
Medicines regulation

Regulatory systems in India

An important global hub for medical products and technologies

India has emerged as a major supplier of medical products globally. In recent years, great progress has been achieved in upgrading health product regulation in India in line with internationally accepted standards. This article gives an overview of the regulatory system in India and some recent initiatives that will make regulatory operations more efficient to ensure effective control and facilitate cooperation with other agencies. There is also the link to universal health coverage, the underlying theme being access to affordable and quality medical products. The country is playing an important role in the global landscape and is called by some “the pharmacy of the world”.

Introduction

The role of a proactive Indian national regulatory authority (NRA) is important in facilitating access to good quality, safe medical products worldwide. Medical products (medicines, vaccines, diagnostic, devices) are critical for achieving the goals of the 2030 Agenda for Sustainable Development, and in particular Goal 3: “Ensure healthy lives and promote well-being for all at all ages”.

The Indian pharmaceutical industry has achieved an eminent global position and has been witnessing phenomenal growth in recent years. India is the third largest pharmaceutical market in terms of volume and thirteenth largest in terms of value, and is expected to grow further rapidly in coming years. The industry covers conventional as well as biological medicinal products including vaccines, pharmaceuticals, and medical devices.

India is emerging as a world leader in generic pharmaceuticals production, supplying 20% of the global market for generic medicines. Indian exports are

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destined to more than 200 countries around the globe including the highly regulated markets of the United States (U.S.), Western Europe, Japan and Australia. India is also a major vaccine producer with 21 major vaccine manufacturing facilities. The vaccines are used for the national and international market (150 countries) which makes India a major vaccine supplier across the globe.

The progress made in developing the pharmaceutical industry in India has increased the importance of its role both in domestic and export markets. However, one may speculate that the industry has developed somewhat more rapidly than the regulatory system. Thus, India is committed to building a strong, world class regulatory system.

India has a functional regulatory system for vaccines according to the criteria of the WHO Global Benchmarking Tool. This is a prerequisite for India-based vaccine manufacturers to apply for WHO prequalification of their products. The functionality of the regulatory authority was confirmed in February 2017 in a comprehensive WHO review of the NRA and affiliated institutions. India is supplying several prequalified vaccines to UN agencies, and this is expected to lead to more affordable vaccines being available on the global market. (2)

Indian manufacturers are the key contributors to the WHO prequalification of medicines programme, with 64% of the finished pharmaceutical products and 59% of the active pharmaceutical ingredients listed on WHO’s prequalification lists being produced in India. Recently, India has played a pivotal role in scaling up access to affordable hepatitis C medicines, and the first WHO-prequalified generic hepatitis C medicine is produced by an Indian manufacturer.

The government has invested large funds for strengthening the drug regulatory authority and drug testing laboratories in the 12th Five Year Plan of the Government of India (2012–17), enabling a range of initiatives and achievements in the regulatory sector. The government has recently invested US$ 275 million for strengthening the drug regulatory system in the country. There is also an upcoming National Drug Regulatory Academy for training of the regulators at central and state levels. (3) India is actively engaged in the new South East Asia Regulatory Network (SEARN) in a move to increase access to high-quality medical products in WHO Member countries in the South-East Asia Region.

The following sections provide an overview of the regulatory landscape of India, and of recent initiatives for regulatory systems strengthening in line with international standards.

Regulatory system

Legal basis
The Indian drug regulatory system originated in 1940, when the Drugs & Cosmetics Act was passed to address the sudden and rapid expansion of pharmaceutical production in the country. The Drugs Rules were framed in 1945 to give effect to the provisions of the Act. (4) Both the Act and Rules were subsequently amended many times, and various legislative texts were passed to regulate the import, manufacture, distribution and sale of drugs in India, including:

- The Pharmacy Act 1948;
- The Drugs and Magic Remedies (Objectionable Advertisements) Act 1954;
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Figure 1: Regulatory environment for health products in India

<table>
<thead>
<tr>
<th>Ministry of Health and Family Welfare</th>
<th>Department of Pharmaceuticals and Fertilizers</th>
<th>Ministry of Commerce</th>
<th>Ministry of Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directorate General of Health Services (DGHS) Indian Council of Medical Research (ICMR)</td>
<td>National Pharmaceutical Pricing Authority (NPPA): Drugs (Prices Control) Order (DPCO) 2013</td>
<td>Patent Office</td>
<td>Department of Biotechnology (DBT)</td>
</tr>
<tr>
<td>+ Statutory Committees + Advisory Committees + State Licensing Authorities</td>
<td>Controller General of Patents</td>
<td>Council of Scientific and Industrial Research (CSIR) Laboratories</td>
<td>Environmental clearance for manufacturing</td>
</tr>
</tbody>
</table>

• **Statutory Committees**: Drugs Consultative Committee (DCC) provide advice on technical matters and on making rules, and Drugs Technical Advisory Board (DTAB): securing uniform implementation of DCA and rules throughout India.

• **Advisory Committees**: Subject Expert Committees (SEC) drawn from relevant panels of experts advise on approvals of clinical trials, drugs and medical devices. New Drug Advisory Committee (NDAC) headed by Secretary, Department of Health Research, and Investigational New Drugs Committee (INDC) headed by Director General of ICRR, provide recommendations on approval of clinical trials.

The Indian Council of Medical Research (ICMR) provides assistance in evaluation of Phase I clinical trials. Three-tier system for examination of clinical trials: NDAC/INDC / Technical Committee (TC) under chairmanship of DGHS / Apex Committee under the chairmanship of Secretary Health.

• For biologicals: Department of Biotechnology (DBT) supports DCG (I) in identifying, formulating, implementing and monitoring of various activities related to biotechnology e.g. through Division of Biologicals and the Cellular Biology-Based Therapeutic Drug Evaluation Committee (CBBTDEC).

• For medical devices (except investigational ones): Medical Devices Advisory Committee (MDAC) advises DCG (I) on review and approval of products and clinical trials

• The Narcotic Drugs and Psychotropic Substances Act 1985;
• The Medicinal and Toilet Preparations (Excise Duties) Act 1956;
• The Drugs (Prices Control) Order (DPCO) 1995 (under the Essential Commodities Act), amended in 2013 to cover specified dosages and strengths under the National List of Essential Medicines (NLEM) 2011 and modified to include medicines in NLEM-2015;
• The National Pharmaceutical Pricing Policy, 2012 (NPPP-2012);
• The Patent Act Amendment 2015 (includes amendments in the Patent Act 2002); and
• The National Health Policy 2017.

Today, most of the Indian health products are governed by the Drugs & Cosmetics Act, which covers a wide variety of drugs, therapeutic substances, diagnostics and medical devices. The regulatory mechanisms and are in line with relevant technical guidelines from international organizations such as WHO, the International Council on Harmonization of Technical Requirements...
Regulatory systems in India

for Registration of Pharmaceuticals for Human Use (ICH), the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and others.

Regulatory environment
The regulatory environment in India is composed of several important stakeholders in the fields of biotechnology, biomedical sciences, agriculture, health care, animal sciences and environment industry (Figure 1).

International collaboration
India has actively contributed and provided support for the new South East Asia Regulatory Network (SEARN). The Indian national regulatory authority is also a member of the Developing Country Vaccine Regulators’ Network (DCVRN); an observer in ICH, and a Vice-Chair of WHO’s Member State Mechanism on substandard and falsified medical products1. Mutual agreements and memoranda of understanding have been concluded with the NRAs of the United States, the United Kingdom, Japan, Russia, Sweden and other countries.

Regulatory authority
India is a federal union of 29 states and 7 union territories. Thus, the Indian drug regulatory system is divided into central (federal) and state (provincial) authorities.

Central Licensing Authority
The national regulatory authority of India is the Central Drugs Standard Control Organization (CDSCO) under the Directorate General of Health Services of the Ministry of Health & Family Welfare. CDSCO is headed by the Drugs Controller General of India, DCG (I). CDSCO has 379 staff members. There has been a steep rise in recruitment, and staffing increased from 111 positions in April 2008 to 474 sanctioned positions currently.

The mission of CDSCO is to safeguard and enhance public health by assuring the safety, efficacy and quality of drugs, cosmetics and medical devices. CDSCO discharges the functions assigned to the central government under the Drugs & Cosmetics Act.(4). The major functions of CDSCO are:

- Frame policy and procedures for uniform implementation of the provisions of Drugs & Cosmetics Act, 1940 and Rules, 1945 thereunder.
- Assist in setting and implementation of standards for Drugs, Cosmetics and Medical Devices through it.
- Coordinate and liaise with international organizations/bodies such as WHO, the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, the European Directorate for the Quality of Medicines & Healthcare (EDQM), the South Asian Association for Regional Cooperation (SAARC), the WHO Regional Office for South East Asia (SEARO), BRICS nations – Brazil, Russia, India, China and South Africa – and other counterparts.
- Exercise regulatory control over the import of medicines, approval of new medicines and clinical trials, conduct meetings with the Drugs Consultative Committee (DCC) and Drugs Technical Advisory Board (DTAB), and act as Central Licence Approving Authority (CLAA) for approval of certain licences.
- Carry out joint inspections through the Zonal Offices and coordinate actions

1 http://apps.who.int/gb/SSFFC/
with the state Drugs Controllers under their jurisdiction.

- Exercise quality control of imported medicines through the port offices.
- Maintain drugs testing laboratories for testing of samples.

CDSCO has a number of affiliated institutions under its control (Figure 2). These include the Central Drugs Laboratory (CDL) in Kasauli, Himachal Pradesh state and the Pharmacovigilance Programme of India at the Indian Pharmacopoeia Commission (IPC) in Ghaziabad, Uttar Pradesh state. CDSCO has six Zonal Offices, five Sub-Zonal Offices (including one created recently at Indore in Madhya Pradesh state) with another being established at Guwahati in Assam state, 13 port offices and eight laboratories under its control. The Zonal Offices work in close collaboration with the state Drug Control Administrations and assist them in securing uniform enforcement of the Drugs & Cosmetics Act and related legislation on an all-India basis. Quality control of imported medicines is performed by the port offices, where samples are taken and forwarded to the drug laboratories for testing.

The main statutory function of the laboratories\(^2\) is to perform analytical quality control as part of quality monitoring performed by the regulatory authorities for imported medicines and those manufactured within the country. Other functions of the laboratories are to undertake analytical research on standardisation and methodology of pharmaceutical products and cosmetics; undertake analysis of cosmetics survey samples received from CDSCO, and quick quality control analysis of life-saving medicines on an all-India basis received from CDSCO Zonal Offices under the National Survey of Quality of Essential Drug Programme.

The Indian Pharmacopoeia Commission (IPC), which hosts one of the three WHO-prequalified medicines quality control laboratories in India, is also involved in testing of imported and new pharmaceuticals. The laboratory has special functions as it is also engaged in preparation and maintenance of national reference standards, training of drug analysts and regulators in quality control analysis, and


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**Figure 2: CDSCO and affiliated institutions**

Central Drugs Standard Control Organization (CDSCO)
Headquarters (HQ) New Delhi

**Zonal Offices**

1. North Zone: Ghaziabad
2. South Zone: Chennai
3. East Zone: Kolkata
4. West Zone: Mumbai
5. Ahmadabad Zone
6. Hyderabad Zone

**Sub-Zonal Offices**

7. Bangalore
8. Chandigarh
9. Jammu
10. Goa
11. Indore (recently created)
development of analytical specifications for preparation of monographs of the Indian Pharmacopoeia.

State Licensing Authorities
At the state level, authorities consist of Food and Drug Administrations (FDA) – one for each state – and certain licensing authorities for the Union Territories (i.e. areas administered by the Union Government directly). The regulation, manufacture, sale and distribution of drugs are primarily the concern of state authorities. The state FDAs also control the quality of food articles, manufactured and sold within the state as well as manufactured outside the state but sold in the state. The functions of the State Licensing Authorities include: (6)

- Licensing of manufacturing site for drugs including API and finished formulation;
- Licensing of establishment for sale or distribution of drugs;
- Approval of drug testing laboratories;
- Monitoring of quality of drugs and cosmetics marketed in India;
- Investigation and prosecution in respect of contravention of legal provision; and
- Recall of substandard drugs.

Regulatory system strengthening

Resources
There has been a steep rise in budget allocation for regulatory strengthening at central and state levels in India. For the financial year 2012-2013 the budget allocation was Indian Rupee (INR) 0.58 billion (approx. US$ 8.7 million), which was raised to INR 4.3 billion (approx. US$ 64.8 million) in the financial year 2015–16.(7) The 12th Five Year Plan envisages a total of 17.5 billion INR (approx. US$ 273 million) for strengthening the drug regulatory structures both at central level3 and state level4.(8)

The increased investments have led to strengthened regulatory manpower, infrastructure, systems and processes. There is provision for scaled-up manpower, new laboratories, an E-Governance portal and a National Drug Regulatory Academy for training of regulators at central and state levels, as described below.

Quality management system (QMS)
There is an established QMS at CDSCO and its affiliated institutions. A quality policy has been established and there are documented quality manuals, standard operating procedures and instructions. Trainings and learning are planned and organized under an institutional development plan. The outcomes of engagements and regulatory processes are published on the website to ensure transparency. Target timelines are established for regulatory processes.

Resource allocation for the QMS is from the Quality Assurance (QA) Division and Biological Division. There is well-established coordination with other institutions, teams and departments/divisions. The Quality team is composed of the respective Divisional Head and staff along with QA Department. Their major functions are to undertake internal and external audits and to obtain ISO certification. Certification under ISO 9001-2008 has been achieved by CDSCO Headquarters, the Zonal Offices of Ahmedabad, Hyderabad, Ghaziabad
and Kolkata, and the Sub-Zonal Office Chandigarh.

**E-governance**

An E-governance system has been launched in India through a portal named SUGAM\(^5\) – literally meaning “ease” or “facilitation” – for on-line processing of applications. The system links the CDSCO headquarters with other offices, laboratories and state authorities. The following CDSCO activities are currently performed through the SUGAM portal:

- Import registration and licensing of drugs and medical devices
- Registration of cosmetics
- Registration of ethics committees
- Permission to conduct clinical trial
- Permission to conduct bioavailability and bioequivalence study for export purpose
- Personal permit for import of drug by individual patient
- Test licence for import of small quantities of drugs for test and analysis purpose.

On-line processing of protocols at CDL, Kasauli and of bills of entries at all CDSCO port offices have been integrated with the customs online system called ICEGATE. The SUGAM portal will also be linked to the state regulatory authorities for online issuance of licences.

The SUGAM portal has been awarded the Computer Society of India (CSI)’s Nihilent e-Governance Award of Excellence 2016.

**WHO Certification Scheme**

The WHO-recommended Certificate of Pharmaceutical Product (CPP) format\(^6\) serves to establish the status of a pharmaceutical product and of the applicant for the certificate in the exporting country. It is issued for a single product only, since manufacturing arrangements and approved information for different dosage forms and different strengths can vary. A CPP is a legal requirement in many countries for imported products submitted for marketing authorization.

After each joint CDSCO and state licensing authority inspection of the manufacturing plant, the drug regulator issues a CPP. Currently 1314 manufacturing units and 10 Ayurvedic manufacturers in India have been granted CPPs for their products.

**Training**

CDSCO and the Ministry of Health & Family Welfare are continuously engaged in imparting training to the drugs regulatory officials and laboratory personnel at central and state levels. Thirty-six training programmes/workshops on the various subjects related to the drug control were held in 2014–15. From October 2015 to May 2017, 10 training programmes including induction as well as advanced-level programmes were organized, about 700 officials were trained. The approved training schemes also entail setting up a National Academy for Drug Regulators.\(^1\) Based on the WHO NRA strengthening Institutional Development Plan, several capacity-building activities focusing primarily on the regulatory inspection function had been organized by WHO during the past years, including several basic as well as advanced workshops for conducting Good Manufacturing Practices (GMP) inspections using a quality risk approach.

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5 https://cdscoonline.gov.in/CDSCO/homepage
Regulatory systems in India

Regulatory functions

Control of clinical trials
Good Clinical Practices (GCP) is an ethical and scientific quality standard for designing, conducting and recording clinical trials that involve the participation of human subjects. Compliance with this standard provides assurance to public that the rights, safety and well-being of trial subjects are protected, consistent with the principles enshrined in the Declaration of Helsinki, and ensures that clinical trial data are credible.

The Indian GCP guidelines (9) were formulated by an Expert Committee set up by CDSCO in consultation with clinical experts, and endorsed by Drug Technical Advisory Board (DTAB). The guidelines are intended to ensure uniform quality of clinical research throughout the country and generate data for registration for new drugs before use in the Indian population.

The role of CDSCO is to review, evaluate and approve or reject clinical trial applications, inspect clinical trial sites, register and monitor ethics committees, and decide on compensation in case of serious adverse events related to clinical trials.

Clinical trial approvals are granted by the Drugs Controller General of India (DCGI), in line with Schedule Y of the 1940 Drugs & Cosmetics Act. An applicant who wishes to conduct a clinical trial has to submit an application to the DCGI along with full product details, animal pharmacology and toxicity data, animal toxicology and clinical data (if available), the trial protocol, and information about the regulatory status of the product in other countries. Applicants also have to report any suspected or unexpected serious adverse reaction (SUSAR) of the product in other countries.

It is the responsibility of the institutional ethics committees (IECs) to review and monitor clinical trials for compliance with ethical guidelines. The role of the IECs is to review the safety reports, the informed consent document, and any violations of the ethical guidelines.

The Indian Council of Medical Research (ICMR)’s 2006 Ethical guidelines for biomedical research on human

Table 1: Timelines for registration & marketing authorization functions

<table>
<thead>
<tr>
<th>Type of Application</th>
<th>Target timeline (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Trial</td>
<td>180</td>
</tr>
<tr>
<td>Marketing Authorization</td>
<td>180</td>
</tr>
<tr>
<td>Registration Certificate for Import</td>
<td>270</td>
</tr>
<tr>
<td>Form 28-D (Manufacturing Licence)</td>
<td>60</td>
</tr>
<tr>
<td>Form 29 Non-Objection Certificate (NOC)</td>
<td>60</td>
</tr>
<tr>
<td>(Licence to manufacture Pre-approval batches)</td>
<td></td>
</tr>
<tr>
<td>Validity of the permission to manufacture pre-approval batches has been increased from 1 year to 3 years</td>
<td></td>
</tr>
<tr>
<td>Import Licence (Form 10)</td>
<td>45</td>
</tr>
<tr>
<td>Test Licence (Form 11)</td>
<td>45</td>
</tr>
<tr>
<td>Validity for import of reference/test/investigational vaccines has been increased from 1 year to 3 years</td>
<td></td>
</tr>
<tr>
<td>Export NOC for Biological Samples</td>
<td>45</td>
</tr>
<tr>
<td>Post Approval Change (Major)</td>
<td>180</td>
</tr>
<tr>
<td>Post Approval Change (Minor)</td>
<td>90</td>
</tr>
</tbody>
</table>
Participants (10) have been accepted as the standard operating manual by IECs in India. A proposed update to these guidelines was finalized for public comment at regional and national consultation meetings jointly organized by ICMR and the WHO Country Office for India in 2016. ICMR also maintains the Clinical Trials Registry of India (CTRI),7 a primary registry under the WHO International Standards for Clinical Trial Registries (ICTRP).8

Various achievements have promoted the scientific and ethical conduct of clinical trials in India. Additional requirements have been introduced for the informed consent process, and audio-visual recording has become mandatory to protect vulnerable subjects in line with international best practice. A three-tier system of scrutiny of proposals of clinical trials by the New drugs Subject Expert Committee (SEC)/Investigational New Drugs Committee (INDC), under the Chairmanship of Directorate General Health Services and Apex Committee under the chairmanship of Secretary Health, has been established (see also Figure 1). Since 2011, registration of ethics committees with the licensing authority is mandatory. New rules are in place for inspections of clinical trials. A rationalized definition of injury has been introduced, and – for the first time in the world by any regulator – exact procedures have been specified for payment of compensation, based on a formula, to subjects to cases of injury or death occurring on account of clinical trials.

A handbook on clinical trial applications was published in January 2017, (11) and training of Subject Expert Committee members and CDSCO reviewers has been stepped up.

Timelines for review of clinical trial applications have been reduced with the expansion of Subject Expert Committee panels and the introduction of an online submission process. Timelines for serious adverse event reporting by investigators, ethics committees and Sponsors have also been rationalized. For clinical trials of recombinant DNA-derived products a parallel submission process to Review Committee on Genetic Manipulation (RCGM) and CDSCO has been introduced.

Registration functions and timelines
Registration and marketing authorization in India includes various processes. An important addition was the amendment of the Drugs & Cosmetics Rules to require bioavailability/bioequivalence studies studies for oral formulations of drugs belonging to the biopharmaceuticals classification System (BCS) Class II and IV before licensing.

Target timelines have been set for the different functions related to marketing authorization (Table 1). In recent years there has been a reduction of the timelines for regulatory approvals. A timeline of 30 working days has been specified for the CDL, Kasauli to review and provide opinion on Module 3 of the Common Technical Dossier (CTD) submitted as part of marketing authorization applications. Approval processes have been simplified as the Subject Expert Committees have to communicate their recommendations on approval of clinical trials and marketing authorizations within five working days.

GMP and regulatory inspections
Inculcating good manufacturing practices (GMP) for pharmaceutical or biological products is an essential regulatory

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7 http://ctri.nic.in/Clinicaltrials/cont1.php
8 http://www.who.int/ictrp/en/
function. Since a consumer cannot detect whether a medicine s/he is taking is safe and effective, it is important that products are manufactured under conditions and practices required by GMP regulations.

Most of the GMP requirements in India are specified under the “Schedule M” of the Drugs & Cosmetics Act 1940. Schedule M specifies the GMP requirements for products such as pharmaceuticals, medical devices and vaccines, and gives detailed specifications on infrastructure, premises, environmental safety, health measures, production, operation controls, quality control, quality assurance, stability, validation and other related areas. The protocols under Schedule M have been amended many times to harmonize it with internationally accepted standards such as WHO-GMP and U.S. FDA guidelines.

GMP inspections of manufacturing units are carried out by qualified inspectors from CDSCO along with inspectors from state Drug Control and product experts from CDL. Inspections are conducted for 2–5 days depending on the size of the unit, the number of products handled and the complexity of products and procedures. Various types of inspection are conducted, including: Pre-approval inspection of the site for grant or renewal of licence; routine annual inspection; for-cause inspection /complaint investigation; inspection subsequent to post approval changes; risk-based inspection; and inspection for issuance of a Certificate of Pharmaceutical Product (CPP) for the purpose of export. Inspections are planned on a risk basis.

The regulatory actions for non-compliances are defined in Rule 85 of the Drugs & Cosmetics Rules and include regulatory letters requiring measures to address the deficiencies, suspension or cancellation of licences and legal prosecution of the manufacturer.

**Licensing of premises**

Under the Drug and Cosmetics Act (4) the regulation of manufacture, sale and distribution of medicines is primarily the responsibility of the state authorities. DCG (I) is responsible for approval of licences of specified categories of products, *i.e.*, biological products including vaccines, blood and blood products, I.V. fluids and notified medical devices. Rule 68-A provides for Grant or Renewal of Licences by the Central Licence Approving Authority.

Both the state and central authorities have adequate competent staff to perform licensing of premises and control activities. 179 drugs inspectors are working in CDSCO, recruitment of additional inspectors is under way and a new post category of Assistant Drugs Inspectors (ADIs) has been created. Approximately 1333 inspectors work in the state authorities.

**Control of imported products**

The CDSCO regulates the quality of medicines imported into the country, including registration of overseas manufacturing sites and drug products including both bulk drugs and finished formulations. The quality of imported medicines is further monitored at the port offices. For imported cosmetics, registration was initiated from 1st April, 2013 to ensure that products are of standard quality and have been manufactured under GMP by genuine, licensed manufacturers. In 2014, the Drugs & Cosmetics Rules were amended to prohibit the testing of cosmetics on animals, and in the same year the prohibition was extended to imported cosmetics.
Market surveillance and control
CDSCO and state authorities fulfil this function as provided in laws, rules and guidance documents, and as agreed in Drugs Consultative Committee meetings. There are designated inspectorates at state and central level, and port officers controlling import and export of products. A state inspector in each district performs sampling; central inspectors also do risk-based sampling. If products are found to be not of standard quality, investigations are carried out and appropriate actions taken such as suspension or cancellation of licences, launching of prosecution, and recalls. Guidelines on Recall and Rapid Alert System for Drugs (12) and on Good Distribution Practices for Biological Products (13) have been circulated all over the country.

During 2014-2016 the Ministry of Health & Family Welfare undertook the largest-ever survey in the world for determining the quality of pharmaceuticals. As part of this survey, 47 954 drug samples relating to 23 dosage forms were drawn from 654 districts of 36 states and union territories from the supply chains including retail outlets and government sources and from eight airports and sea ports. In many ways, this Survey of Extent of Problems of Spurious and Not of Standard Quality Drugs in the Country was the first of its kind, and the largest ever scientifically designed and professionally executed drugs survey conceptualised to understand the quality of drugs being sold in the domestic market of India. The survey found that 3.16% of the samples tested were Not of Standard Quality (NSQ), and 0.0245% were spurious.(14)

Control of promotional materials
Unlike package inserts of drugs, promotional materials are not pre-approved. However, false claims or advertisements are detected by random checks and complaints and are punishable under general law and under the Drugs and Magic Remedies (Objectionable Advertisement) Act, 1955.

Pharmacovigilance
WHO has been playing a pivotal role in supporting health product regulation in India at both central and state levels, particularly in strengthening the vigilance of medical products. The Indian Pharmacopoeia Commission (IPC) has recently been designated as the first WHO Collaborating Centre for capacity-building for pharmacovigilance in public health programmes and regulatory services in the WHO South-East Asia Region.(15)

Medicines
The Pharmacovigilance Programme of India (PvPI) was initiated by CDSCO in 2010. Its functions are to create a nationwide system for ensuring patient safety through better adverse drug reaction reporting; to identify and analyze new signals on adverse drug reactions (ADRs) from reported cases; to analyze the benefit/risk ratio of marketed medications; to support regulatory agencies in the decision-making process on use of medications; to communicate the safety information on use of medicines to various stakeholders to minimize risks; to collaborate with other national centres for the exchange of information and data management; and to provide upon request training and consultancy support to other pharmacovigilance centres globally.

PvPI has a Steering Committee, several Working Groups and three panels for Signal Review, Quality Review and Core Training. The Signal Review Panel (SRP) periodically analyzes individual case safety reports (ICSRs), identifies safety signals and...
Regulatory systems in India

provides recommendations on any needed regulatory actions to CDSCO.

Reports on suspected ADRs can be submitted by health care professionals and consumers. Drugs & Cosmetics Act & Rules was amended by Gazette notification GSR no. 287 (E) dated 8th March 2016, mandating all manufacturers and importers for setting up a pharmacovigilance system managed by qualified and trained personnel within their company.

Most reports are received from local ADR Monitoring Centres (AMCs). The Programme started with 22 AMCs and as on January 2017 has 210 centres across the country. Of these, 17 receive information from the Revised National Tuberculosis Control Programme (RNTCP), 20 from the HIV control programme on anti-retroviral therapy, and 6 are designated as Bedaquiline Centres. The recent PvPI focus on cohort event monitoring of bedaquiline is a classic example of a response to newer drugs of national importance.

The ICSRs collected under PvPI are also submitted into the WHO global database of adverse drug reactions called Vigibase.\(^9\) Vigibase is hosted by the WHO Collaborating Centre for International Drug Monitoring – Uppsala Monitoring Centre (UMC).

Vaccines

A surveillance programme to monitor adverse events following immunization (AEFI) was initiated in India in 1988. In 2005, the Government of India, with technical assistance from WHO, drafted the National AEFI Surveillance and Response Operational Guidelines, which were subsequently revised in 2010 and 2015.\(^{16}\)

Vaccine pharmacovigilance in India is handled in close cooperation by three partner agencies: CDSCO, the AEFI Division under the Ministry of Health & Family Welfare, and the IPC’s PvPI. Many public sector AEFI surveillance workshops have been conducted throughout the country. A QMS has been established, guidance documents and standard operating procedures published, training provided, and a pilot online reporting project introduced. As a result, AEFI reports have increased from 398 in 2012 to 1393 in 2016. However, AEFI surveillance in the private sector is still very limited and needs attention, as it also contributes a critical part in the immunization process.

The Pharmacovigilance Division (Human vaccine) within CDSCO’s Biological Division monitors all post-licensure activities for vaccines including reporting of AEFI, periodic safety update reports (PSUR) and any other data on adverse reactions. CDSCO decisions are taken based on analyses of these data by an expert committee, recommendations from the National AEFI Committee, and investigations including testing of samples as and when required. On the recommendations of the PSUR expert committee CDSCO will generally request marketing authorization holders to set up a pharmacovigilance system within their company, to conduct active surveillance for collection of AEFI data, and/or to update package inserts to include any additional warnings or information as appropriate.

Blood products

The Haemovigilance Programme of India (HvPI)\(^{10}\) was launched in 2012 as a fundamental component of the Pharmacovigilance Programme of India (PvPI). Its objective is to monitor


\(^{10}\) [http://www.nib.gov.in/haemovigilance.html](http://www.nib.gov.in/haemovigilance.html)
adverse events related to blood products all along the transfusion chain. Currently, 154 centers have been enrolled in this programme. Information obtained is filled in the Transfusion Reaction Reporting Form (TRRF) and transmitted to the National Coordinating Centre at the National Institute of Biologicals (NIB) using the Hemovigil® software. The NIB’s recommendations based on the collected data are forwarded to the National Coordinating Centre at IPC for further transmission to CDSCO.

The haemovigilance programme is functional through a core group and an advisory committee, which coordinate the haemovigilance activities between medical colleges and the National Coordinating Centre and provide expert opinions for analysis of the information generated. The advisory committee also provides helpful insights in linking HvPI with the International Hemovigilance Network (IHN).

**Regulation of medical devices**

The medical devices sector is one of the 25 focus sectors identified under the “Make in India” campaign, which was launched in 2014 by the Indian government to make India a global manufacturing hub and bring foreign technology and capital into the country. Similarly, the National Medical Device Policy 2015 aims at reducing dependence on imports of medical devices and equipment. To facilitate investments the Cabinet has allowed foreign direct investment of up to 100% under the automatic route for manufacturing of medical devices subject to specified conditions.

Various initiatives are under way to promote the medical device industry. A scheme for financing common facility centres at medical device parks is under consideration under the umbrella of the “Development of Pharmaceuticals Industry” scheme to create an ecosystem for high-end medical device manufacturing and import substitution with an eye on the for-export market. Corrections have been introduced in the inverted duty structure: Import duty on certain product categories has been raised and exemption from special additional duty (SAD) withdrawn, while basic customs duty has been reduced and SAD waived on raw materials. Furthermore a proposal is under consideration for giving preference to domestic manufacturers in purchase of medical devices by government agencies. A Uniform Code for Medical Device Marketing Practices has been drafted for comment by stakeholders. Lastly, a proposal is under consideration to set up a Medical Device Promotion Council at Vishakhapatnam in co-operation with Andhra Pradesh MedTech Zone Ltd. (AMTZ). The Council will act as a facilitating and promotional body for domestic medical devices.
These moves are strongly supported by the recently notified regulatory framework for medical devices, which will come into force on 1 January 2018. It is encouraging that this framework is based on international standards. The new Rules have been framed in conformity with the Global Harmonization Task Force (GHTF) framework in line with best international practices. The amended Drugs & Cosmetics Act will also regulate the import, manufacture, distribution and sale of medical devices.

Monitoring of adverse events related to medical devices, including in vitro diagnostic products, is an important component of regulatory control, as their performance depends to a considerable extent on their appropriate use. A system is in place for this purpose through the Materiovigilance Programme of India (MvPI), launched in 2015 under the umbrella of PvPI. There are 10 Medical Device Monitoring Centres (MDMCs). Adverse events are reported by a wide range of stakeholders supplying or handling CDSCO-notified medical devices. Reports are recorded on the Medical Device Adverse Event (MDAE) reporting form, which is forwarded by the MDMCs to the National Collaboration Centre. IPC receives technical support from the National Health System Resource Centre (NHSRC) and collaborates with the Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST) in providing advice to CDSCO on regulatory actions for medical devices.

The Indian medical device sector continues its upward march of growth and is strongly supported by India’s robust notified regulatory framework, including the Materiovigilance Programme of India (MvPI) described above which has been formulated by the Government of India as a system of reporting of adverse events related to medical devices.(17)

Conclusions
India’s pharmaceutical market has expanded rapidly, and India is increasingly important for the production of vaccines, generic medicines and other pharmaceutical products. Improving access to medical products is central to the achievement of universal health coverage. Strategies to improve access also need to be linked to the safety and quality assurance of all medical products. The need to expand access to medicines and health products is highlighted in the United Nations’ Sustainable Development Goals (SDGs) specifically in two targets and more broadly in at least seven other targets under Goal 3 of the SDGs.

Access to health products will be a key indicator for countries’ progress to universal health coverage. This gives an opportunity to build on progress made so far and help to bring about access to quality essential medicines and health products for all.

Developing and supporting regional networks for regulatory cooperation and building capacity of national regulatory authorities will be a major element of this priority. India has actively contributed and provided support for the new South East Asia Regulatory Network (SEARN) in a move to guarantee access to high-quality medical products in the WHO South-East Asia Region Member countries.

There have been many examples of the Indian government’s commitment towards strengthening the regulatory systems of the country. India also has to its advantage access to a pool of highly skilled
scientists and R&D facilities that can help in developing novel products with lower production costs.

Health care has become one of the key priorities of the Indian Government, and new policies and programmes have been launched to boost local access to affordable, quality health care. The Union Budget 2017–18 shows an increase of 23% in health expenditure that is likely to give further impetus to the pharmaceutical sector. The government, as part of the Budget, has proposed amendments to the Drugs & Cosmetics Rules to ensure availability of generic drugs at reasonable prices and promote their use. The government has also introduced a range of fiscal incentives to promote domestic manufacturing, including the reduction of inverted duty structure and basic customs duty.

A robust medical products regulatory system in India can help the country realize the Prime Minister’s vision of “Make in India” and channel political commitment and resources in this important direction. It is important to point out that regulatory systems strengthening is an integral part of overall health systems strengthening which is vital for achieving medical products related Sustainable Development Goal 3: Good Health and Well-being, and WHO aspirations of achieving Universal Health Coverage (UHC). In conclusion, we believe that building up a modern, robust and efficient regulatory system in India is a good investment in public health not only for Indians but also globally.

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WHO prequalification

Prequalification process quality improvement initiatives: 2010–2016

In the past six years the WHO Prequalification Team (WHO-PQT) has organized a total of four surveys to evaluate client satisfaction among manufacturers that have applied for prequalification of their medicines, vaccines or in vitro diagnostic products. This article provides an overview of the survey findings and some other initiatives to improve prequalification process quality.

WHO prequalification remains an important pathway for quality assurance of key medical products purchased by UN agencies, national agencies and international organizations. The sustainability of the prequalification programme is critically dependent on manufacturers’ continued participation. Survey results assist WHO-PQT in designing and implementing targeted improvements to its services.

Background
Ensuring the quality of health products is the responsibility of national regulatory authorities (NRAs). Given the varying regulatory capacity of WHO Member States, WHO provides a “quasi-regulatory” service to identify health products – including affordable generics – that are acceptable for use in UN-funded health programmes. WHO prequalifies vaccines (since 1987), selected medicines for treating priority diseases (since 2001) and selected in vitro diagnostics (IVDs) (since 2010, building on an earlier programme). Prequalification of vector control products to prevent malaria was launched in 2016, and the first invitation for prequalification of selected biosimilars to treat cancer is planned to be issued before the end of 2017.

Prequalification is based on WHO-recommended norms and standards and is performed by the Prequalification Team (WHO-PQT). Regulatory experts from a wide range of settings participate in WHO assessment and inspection activities. Processes are in place for risk management, variation control of constantly changing products, and reliance on stringent assessments performed by other regulators. Prequalification of active pharmaceutical ingredients (APIs) and quality control laboratories have been added as supporting services.

While WHO prequalification was initially controversial, WHO-PQT has become part of what could be termed the regulatory community. Prequalification outcomes are recognized not only by UN agencies, but also by many governments and international organizations that procure medical products, and regulatory authorities in many WHO Member States rely on prequalification outcomes in granting marketing authorizations, thus optimizing the use of limited regulatory resources.
Applicant satisfaction surveys
Prequalification is voluntary for manufacturers, and the sustainability of the programme depends on their continued participation. In 2010, WHO undertook a comprehensive review exercise to seek feedback from applicants on the prequalification service for medicines. This was followed by service quality surveys for vaccines in 2011, for diagnostics in 2015, and again for medicines in 2016.

Method
A survey methodology was developed in 2009 to provide a unified framework for measurement of service quality. An online questionnaire was administered to regulatory and quality assurance professionals in manufacturing organizations, covering a range of aspects related to service design and service delivery (Annex 1). The service design indicators were developed as a result of a process review with WHO-PQT staff and interviews with manufacturers. They measured the respondents’ perceptions of the consistency of policies and procedures, feedback mechanisms, resource management, problem-solving options and complaint handling in the various prequalification processes. The service delivery aspects were based on a widely recognized scale of service quality. In addition, narrative feedback was sought.

The service quality aspects covered in the surveys were rated on a 7-point scale, together with the minimum and desired expectations for each respective aspect as provided in any regulatory pathway.

Main findings

Medicines – 2010
The 2010 survey on medicines prequalification found that on the whole, the service provided by WHO assessors and inspectors, and the structure of prequalification itself, were meeting or exceeding manufacturer expectations. Areas for improvement included dossier review timelines, opportunities for in-person communications, problem resolution during assessment, consistency of membership in the assessors team, and inclusion of local/national observers in inspection teams.(2)

Vaccines – 2012
Manufacturers rated the vaccine prequalification service as acceptable. No service area was scored significantly below minimum expectations. The strengths were in those aspects of service delivery that build applicants’ confidence in the prequalification process. Areas for improvement included the structuring of processes and time-related aspects, including both time to prequalification and efficient, predictable time management including for prequalification and sample testing processes.(3)

Vaccine products are eligible for prequalification only if the reference NRA of the producing country is shown to be functional in all aspects of vaccines oversight, as defined in a standardized WHO benchmarking tool. NRAs are therefore important partners in prequalification of vaccines. A separate qualitative study included interviews with five NRAs and three organizations procuring prequalified vaccines. These respondents valued WHO’s expertise and service highly. They suggested that the efficiency of exchange of information should be improved, as this
would help to avoid duplication of processes, facilitate a rapid response to emerging issues, and anticipate future needs. They also appreciated the capacity built in some reference NRAs through prequalification and called for advocacy to promote reliance, stating that only WHO can communicate to recipient countries “why vaccines coming from Thailand are safe.” Some of these suggestions are now being addressed by the WHO-National Control Laboratory (NCL) Network for Biologicals, established in 2016 among NCLs responsible for lot testing of prequalified vaccines.(4)

Diagnostics – 2015
The 2015 survey on IVD prequalification showed that the strength of the programme is in service delivery. The dossier reviewers and site inspectors were found to be competent, dependable, responsive and attentive to each applicant’s situation. On the other hand, the processes for dossier assessment, inspections and laboratory evaluation, as well as timelines, were seen as in need of improvement.

In this survey the respondents’ ratings of prequalification timelines were very diverse. Interestingly, a subgroup analysis showed that those who rated the process as “fast” also had more favourable perceptions of various other aspects of the prequalification process and even of its benefits for the company.

Medicines – 2016
The follow-up survey on medicines prequalification showed that manufacturers were more satisfied with the prequalification service than in 2010. All aspects measured in the survey had average ratings at or above the manufacturers’ expectations for any regulatory pathway; no item had an average score below the minimum required service level. One respondent commented: “The PQ process has improved dramatically over the past 6 years… They are now on the right track.”
The results of the 2016 survey provided evidence that efforts to reduce the time to prequalification have been successful. The timely progress of dossier assessments is now a strength of the programme, although efficient use of time in inspections could be improved further. Significant progress was also noted in terms of training and assistance provided to applicants before and during the prequalification process. Some respondents would like to see more user-friendly means of data submission. Average ratings were somewhat lower, but still met manufacturer’s minimum expectations, with regard to the transparency of selecting products invited for prequalification, as well as a number of aspects related to inspections.

**Key drivers of participation**
Overall the survey findings provided a picture of the main drivers of manufacturers’ continued participation in prequalification, and how these impact each other (Box 1).
In the 2016 follow-up survey on medicines, of the dimensions contributing to overall satisfaction, process design was most important for the respondents, followed by time-related aspects and service delivery. In the 2015 diagnostics survey, satisfaction with time-related aspects also had a direct impact on the perceived benefits of prequalification.

**Enhancing and sustaining prequalification**
In addition to surveying manufacturers regarding prequalification services and incorporating the findings into revised policies and procedures, WHO-PQT initiated other measures to improve the efficiency of its service offerings (Box 2).
New internal metrics (KPIs) have been proposed to measure progress in areas important to stakeholders, and a new website was developed to provide a more user-friendly online experience for visitors. A new prequalification fee structure was also developed to increase programme sustainability.

**Prequalification services in context**
International donors and procurement agencies have harmonized their quality policies, and require either WHO prequalification or stringent regulatory approval for key categories of products that they purchase. In strategic decisions on which pathway(s) to pursue, companies will weigh the cost and time to be invested against the expected benefits in terms of market access. The impact of prequalification timelines as a key driver of manufacturers’ perceptions of benefits is therefore not altogether surprising.

**Box 2: Recent initiatives to enhance prequalification services**

**Timeline-related KPIs**
As in many regulatory systems, prequalification timelines are calculated separately for WHO actions and applicant actions (“stop-clock time”). In July 2017 WHO-PQT proposed a new set of timeline-related key performance indicators (KPIs) for public comment, with a harmonized calculation approach across product categories. The new KPIs will be applied when the new prequalification IT system, currently under development, is launched.

**Website**
A new medicines prequalification website with greatly enhanced search functions was launched in early 2017. A model dossier was also made available on the website. It illustrates how data for finished pharmaceutical products should be submitted to WHO, providing valuable practical guidance to applicants, with added value for regulatory training and harmonization initiatives.
In comparing the service quality of prequalification processes with those of stringent regulatory authorities (SRAs), some of the more intangible benefits may also be considered that result from the different mandates of WHO and SRAs.

Stringent approval, in international procurement, is defined as marketing authorization by a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). These authorities cater mostly for the needs of high-income countries. Mechanisms for assessment of medicines to be used outside the SRAs’ own territories include the U.S. FDA approvals for the President’s Emergency Plan for AIDS Relief (PEPFAR) and the EMA “Article 58” procedure. However, the former applies only to antiretrovirals and the latter has had limited uptake. For IVDs the SRA route also has some limitations: international organizations recognize the relevant authority’s approvals only if they were achieved through the authority’s stringent “high-risk classification” procedures, which typically apply to HIV and hepatitis tests but not malaria or tuberculosis tests.

In the long term, ICH is set to become more relevant to low- and middle-income countries as it is expanding its membership to become a truly global organization. In light of these changes a concept for revising the definition of “stringent regulatory authority” has been proposed. For the time being, however, stringent regulatory processes are mostly designed for products supplied to each SRA’s own territory.

WHO prequalification on the other hand aims to cater for the needs of the Organization’s 194 Member States. Based on WHO’s mandate to serve its Member States globally, prequalification services are geared to provide some added benefits for global suppliers of health products to donor-funded markets:

- **Product suitability in target countries.** Prequalification considers the requirements of products in the settings of their intended use, e.g.: stability of medicines in hot and humid climates, suitability of vaccines in the target countries, or ease of use of diagnostic tests at the point of use.

- **Collaborative oversight.** From its beginnings, WHO has involved regulators from across its Member States in prequalification. This has opened up communication channels that provide added assurance of effective oversight of product quality, which is valued by procurers.

- **Support for market access in target countries.** WHO’s collaborative registration of prequalified medicines and vaccines offers an accelerated pathway for registration in participating countries. And for global suppliers of vaccines the newly established control laboratory network, which aims to promote reliance and reduce redundant lot testing, could remove some significant regulatory hurdles.

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1. [www.fda.gov/internationalprograms/pepfar/ucm119231.htm](http://www.fda.gov/internationalprograms/pepfar/ucm119231.htm). Used frequently but limited to antiretrovirals.

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Example: An African regulator who had worked with WHO-PQT on collaborative initiatives approached WHO about a batch of bilayered tablets found on the local market that differed from the registered specifications with regard to appearance. The WHO-PQT assessors provided advice and requested the WHO-PQT inspectors to take up the issue in their next inspection of the manufacturing site concerned.

See [https://extranet.who.int/prequal/content/collaborative-registration-faster-registration](https://extranet.who.int/prequal/content/collaborative-registration-faster-registration)
Conclusions

WHO prequalification was established to bridge regulatory gaps in Member States by offering all manufacturers, regardless of where they are based, a stringent assessment mechanism for their medical products. But gaps persist, and global regulatory challenges are growing. Even well-resourced regulatory authorities are increasingly dependent on collaboration with other NRAs and reliance on other NRAs' regulatory outputs to perform all regulatory functions.

Clearly there is a continued need for WHO prequalification. In 2014 the World Health Assembly called on WHO and Member States to support the programme. More recently The Lancet's Commission on Essential Medicines Policies commented: “The prequalification programme is a concrete application of WHO's global norms and standards for medicines quality and safety. It has positioned WHO as a global regulatory agency and has greatly shaped the world's generic markets, driving down costs while ensuring the quality of products. It has also become an important training ground for regulators and inspectors, paving the way for regional harmonisation”. It recommended that WHO prequalification should maintain a focus on new essential medicines to help achieve universal health coverage.

WHO prequalification is critically dependent on manufacturers’ continued participation. Encouragingly, the 2016 follow-up survey for medicines prequalification showed that improvements have been made and sustained, and the service provided meets the respondents’ expectations in every respect. Ongoing communication with manufacturers will be critical to ensuring that prequalification services remain attractive for applicants and therefore sustainable for WHO.

References

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Annex 1: Overview of aspects rated in manufacturer surveys

<table>
<thead>
<tr>
<th>Service design – “Process”</th>
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</thead>
<tbody>
<tr>
<td><strong>Assistance to applicants</strong></td>
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<tr>
<td>Transparency on how products are selected/prioritized</td>
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<tr>
<td>Website: Clear guidance on process</td>
</tr>
<tr>
<td>Assessment: Understanding provided of full review process</td>
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<tr>
<td>Inspection: Plan provided with all required information to prepare for inspection</td>
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<tr>
<td><strong>Post-marketing surveillance</strong>: Required information provided for manufacturer to act on complaints</td>
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<tr>
<td><strong>Consistency of policies and procedures</strong></td>
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<tr>
<td>Assessment: Consistent standards applied for quality, safety and efficacy</td>
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<tr>
<td>Inspection: Clear requirements</td>
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<tr>
<td>Laboratory evaluation*: Opportunity to review product testing at the evaluation site prior to actual product testing</td>
</tr>
<tr>
<td><strong>Post-market surveillance</strong>: Clear explanation of obligations</td>
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<tr>
<td><strong>Sample testing</strong>: Clear requirements at time of initial assessment</td>
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<tr>
<td><strong>Problem resolution</strong></td>
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<tr>
<td>Efficient process to resolve issues and questions raised</td>
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<tr>
<td><strong>Assessment</strong>: Opportunities for in-person meetings with assessors</td>
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<tr>
<td><strong>Inspection</strong>: Opportunities to address technical questions/non-conformities</td>
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<tr>
<td><strong>Sample testing</strong>: Addressing manufacturers’ questions on testing results</td>
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<tr>
<td><strong>Time-related aspects</strong></td>
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<tr>
<td>Acceptable overall time to prequalification</td>
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<tr>
<td><strong>Assessment</strong>: Timely screening process</td>
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<tr>
<td><strong>Inspection</strong>: Timely announcements</td>
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<tr>
<td>Laboratory evaluation*: Laboratory evaluation report sent in a timely manner</td>
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<tr>
<td><strong>Post-market surveillance</strong>: Timely handling of complaints</td>
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<tr>
<td>Sample testing**: Time taken to complete the testing</td>
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<tr>
<td><strong>Service delivery – “People”</strong> <em>(Rated separately for assessors and inspectors)</em></td>
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<tr>
<td>Ability to perform the promised service dependably and accurately</td>
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<tr>
<td>Willingness to help applicants and provide prompt service</td>
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<tr>
<td>Knowledge, courtesy and ability to convey trust and confidence</td>
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<tr>
<td>Caring, individualized attention provided to applicants</td>
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<tr>
<td><strong>Perceived benefits</strong></td>
</tr>
<tr>
<td>Internal: Increased internal capabilities of company</td>
</tr>
<tr>
<td>External: Increased access to global markets</td>
</tr>
<tr>
<td><strong>Participation in prequalification</strong></td>
</tr>
<tr>
<td>My company intends to submit additional medicinal products in the future; I expect my company to continue participating</td>
</tr>
</tbody>
</table>

* = For diagnostics only; ** = For vaccines only
Safety news

Safety warnings

**Brimonidine gel:**  
**Systemic cardiovascular effects**  
**United Kingdom** – The MHRA has informed health care professionals that systemic cardiovascular effects including bradycardia, hypotension and dizziness have been reported after application of brimonidine gel. Some patients required hospitalization. In approximately 30% of the cases most strongly suggestive of a cardiovascular effect, events occurred following application after laser therapy to the skin. To minimize the possibility of systemic absorption patients should be warned not to apply brimonidine gel to irritated or damaged skin, including after laser therapy to the skin.

According to the product information, dizziness was reported to occur uncommonly (with an estimated frequency of less than 10 in 1 000 patients treated), while hypotension and bradycardia were reported to occur rarely (in less than 1 of 1 000 patients treated). Brimonidine gel is indicated for the symptomatic treatment of rosacea in adults.

► [MHRA Drug Safety Update volume 10 issue 11, June 2017: 2](#).

**Lactose-containing injectable methylprednisolone:**  
**Do not use in patients allergic to cow’s milk proteins**  
**European Union** – The EMA has recommended against the use of injectable methylprednisolone containing lactose in patients with a known or suspected allergy to cow’s milk proteins. Patients being treated for an allergic reaction with methylprednisolone should have their treatment stopped if their symptoms worsen or if they develop new symptoms. The product information will be revised to reflect these recommendations, and the vials and packaging of these medicines will be clearly marked with a warning.

A review has found that lactose of bovine origin may introduce traces of cow’s milk proteins into the medicine which can trigger reactions in allergic patients. This may lead to additional doses being given, which will further worsen the patient’s condition.

Considering that methylprednisolone is often used in emergency settings where details of patients’ allergies are not always known, the EMA recommended that cow’s milk proteins should be removed from the preparation. Companies have been asked to take steps by mid–2019 to replace current formulations with lactose-free ones.


**Amoxicillin:**  
**Very rare risk of DRESS**  
**Ireland** – The HPRA has informed health professionals that amoxicillin is associated with a very rare risk of drug reaction with eosinophilia and systemic symptoms (DRESS). The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) had reviewed a signal and had recommended that DRESS should
be added to the very rare severe cutaneous adverse reactions mentioned in the product information for amoxicillin-containing medicines.

► **HPRA Drug Safety Newsletter, 82nd Edition. August 2017.**

### Azithromycin:
**Acute generalized exanthematous pustulosis**
**Japan** – The regulatory authorities have recommended updates to the product information for azithromycin-containing products to include the risk of acute generalized exanthematous pustulosis (AGEP). *(1)*

A signal of this risk with azithromycin and three other macrolide antibacterials was also detected in the European Pharmacovigilance Issues Tracking Tool (EPITT) and is under assessment by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC). *(2)*

► *(1) PMDA Summary of investigation results, 3 August 2017. PMDA. Revisions of precautions [webpage].


### Fluconazole, fosfluconazole:
**Drug-induced hypersensitivity syndrome**
**Japan** – The PMDA has informed health professionals that cases of drug-induced hypersensitivity syndrome (also called Drug Reaction with Eosinophilia and Systemic Symptoms, DRESS) have been reported in patients treated with the antifungal medicine fluconazole both in Japan and overseas. The MHLW has recommended to add a warning about this risk to the product information for systemic products containing fluconazole or its pro-drug fosfluconazole. Initial symptoms of drug-induced hypersensitivity syndrome may include fever and rash, followed by serious delayed symptoms of hypersensitivity accompanied by liver function disorder, swollen lymph nodes, increased white blood cells, eosinophilia, and appearance of atypical lymphocytes. In case of such symptoms the medicine should be stopped and appropriate measures taken. This event is often accompanied by virus reactivation, and symptoms such as rash, fever, liver function disorder may persist or recur after treatment is stopped.

► **PMDA Summary of investigation results, 4 July 2017. PMDA. Revisions of precautions [webpage].**

### DAAs and warfarin:
**INR changes**
**New Zealand** – Medsafe has advised health professionals to watch out for INR changes when direct-acting antivirals (DAAs) for hepatitis C (sofosbuvir, daclatasvir, asunaprevir, ledipasvir/sofosbuvir, elbasvir/grazoprevir and the combination products Viekira Pak® and Viekira Pak-RBV®) are used concomitantly with warfarin.

Recent evidence indicates that the use of DAAs together with warfarin may result in changes in international normalised ratio (INR). In most cases decreases in INR were reported. INR should be monitored frequently, and treatment adjusted as needed. Frequent monitoring of INR is also required in the post-treatment period, particularly if any warfarin dose adjustment has occurred.

Medsafe has further advised health professionals to use available tools to check for drug interactions with DAAs, and has reminded them that the overall benefit-risk balance of DAA regimens remains positive. *(1)*
A signal was under assessment by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) in 2016 and product information was updated in the EU. (2)

(2) EMA. PRAC recommendations on signals, 15 September 2016.

**Bendamustine:**
**Risk of opportunistic infections greater than expected**

*United Kingdom* – The MHRA has alerted health professionals that the risk of opportunistic infections for all patients receiving the cancer medicine bendamustine (Levact®), including those receiving off-label treatment, may be greater than previously recognized.

Increased mortality was seen in clinical trials when bendamustine was used in combination treatments outside its approved indications, which include treatment of chronic lymphocytic leukaemia, non-Hodgkin’s lymphoma and multiple myeloma in certain patients. Hepatitis B virus (HBV) reactivation has also been reported. Patients should be advised to report promptly any new signs of infection and should be monitored for opportunistic infections as well as cardiac, neurological, and respiratory adverse events.


**Nivolumab:**
**Sclerosing cholangitis**

*Japan* – The PMDA has informed health professionals about cases of sclerosing cholangitis reported in patients treated with the cancer medicine nivolumab (Opdivo®) in Japan. Sclerosing cholangitis is characterized by swelling, inflammation, scarring and destruction of the bile ducts inside and outside of the liver. The product information for nivolumab in Japan will be updated to include a warning about this risk.

► PMDA Summary of investigation results, 4 July 2017.
PMDA. Revisions of precautions [webpage].

**Nivolumab, pembrolizumab:**
**Organ transplant rejection**

*United Kingdom* – The MHRA has informed health professionals that since November 2016 nine cases of rejection of solid organ transplants, including renal and corneal grafts, have been reported in the post-marketing setting in cancer patients treated with the monoclonal antibodies nivolumab (Opdivo®) or pembrolizumab (Keytruda®) in the EU.

In two cases the adverse events occurred in association with ipilimumab (Yervoy®), which carries a warning that it may interfere with immunosuppressive therapy, resulting in an increased risk of graft rejection.

Health professionals have been advised to consider the benefits of treatment with these medicines against the risk of possible organ transplant rejection for each patient.


**Pembrolizumab:**
**Myeloma clinical trials halted after patient deaths**

*United States of America* – Based on data from two recently halted clinical trials with the anti-cancer medicine pembrolizumab (Keytruda®), the FDA has warned about the risk of increased mortality with this medicine when used in combination with dexamethasone and an immunomodulatory agent (lenalidomide or pomalidomide) for the treatment of patients
with multiple myeloma. Other multiple myeloma clinical trials of pembrolizumab, other PD-1/PD-L1 cancer medicines and other combinations are currently undergoing clinical evaluation.

Pembrolizumab is not approved for treatment of multiple myeloma. The medicine can continue to be used for approved indications, which in the U.S. include melanoma, lung cancer, head and neck cancer, classical Hodgkin lymphoma, urothelial carcinoma and microsatellite instability-high (MSI-H) cancer.

► Statement from CDER Director, 31 August 2017.

**Atezolizumab:**
**Severe cases of myocarditis**

New Zealand – The marketing authorization holder, in consultation with Medsafe, has informed health professionals that cases of myocarditis have been reported in clinical trials with the cancer medicine atezolizumab (Tecentriq¹). Atezolizumab should be withheld for Grade 2 myocarditis, initiation of treatment with systemic corticosteroids may be considered. Atezolizumab should be permanently discontinued for Grade 3 or 4 myocarditis.

Immune-mediated myocarditis is listed in the data sheets of similar-in-class medicines. The data sheet for atezolizumab will be updated to reflect this risk.

► Medsafe Safety Information, 3 August 2017.

**Ibrutinib:**
**Cardiac arrhythmia, hepatitis B reactivation, opportunistic infections**

United Kingdom – The MHRA has alerted health care professionals to new safety issues with the blood cancer medicine ibrutinib (Imbruvica¹) that were identified in a routine European review of the safety profile of ibrutinib in the pre- and post-marketing settings.

Cases of ventricular tachyarrhythmia have been reported in patients treated with ibrutinib. Treatment should be interrupted in patients who develop symptoms such as palpitations, chest pain, dyspnoea, dizziness or fainting. Treatment should only be restarted after the benefit-risk balance has been assessed and found favourable.

Cases of hepatitis B (HBV) reactivation have been reported with ibrutinib. Patients should be tested for HBV infection before treatment initiation. In case of a positive hepatitis B serology a liver disease expert should be consulted, and if treatment with ibrutinib is found necessary patients should be monitored and managed to prevent HBV reactivation.

Opportunistic infections are a known, very common adverse event in patients treated with ibrutinib. Given the relatively high number of fatal cases, healthcare professionals should consider prophylaxis according to standard of care for patients who are at an increased risk of opportunistic infections.

► Drug Safety Update volume 11 issue 1, August 2017: 1

**Daclizumab:**
**Risk of serious liver injury, restrictions**

European Union – The EMA is provisionally restricting the use of daclizumab (Zinbryta¹) because of the risk of severe liver injury. The medicine should only be used in patients with highly active relapsing multiple sclerosis that has failed to respond to certain other treatment, and to patients with rapidly evolving relapsing disease who cannot be treated with other medicines. Patients with liver injury must not be given
daclizumab, and caution should be used when prescribing it together with medicines that can damage the liver. Treatment should not be initiated in patients with autoimmune diseases other than multiple sclerosis. Health professionals should monitor the liver function of patients treated with daclizumab and watch them closely for signs and symptoms of liver injury.

An EU-wide safety review of daclizumab is ongoing. It was triggered following the death from fulminant liver failure of a patient in an observational study as well as four cases of serious liver injury. The risk of liver damage was known at the time when daclizumab was approved in the EU, and several measures were recommended to manage this risk.

Loxoprofen topical preparations: Shock, anaphylaxis
Japan, Korea – Cases of shock and anaphylaxis have been reported in patients treated in Japan with topical formulations of loxoprofen, a nonsteroidal anti-inflammatory drug (NSAID). A warning about this risk will be included in the product information for loxoprofen-containing gels, sprays, tapes and other preparations approved in Japan. Patients should be carefully monitored; in case of any symptoms such as decreased blood pressure, urticaria, laryngeal oedema or dyspnoea loxoprofen should be stopped immediately and appropriate measures should be taken.(1) A similar update is in preparation for loxoprofen-containing products approved in the Republic of Korea.(2)

Denosumab: Osteonecrosis of the outer ear canal
European Union – The approved product information for denosumab (Prolia®, Xgeva®) has been revised to include a warning on the risk of osteonecrosis of external auditory canal. Patients should be advised to report any ear pain, discharge from the ear, or an ear infection during denosumab treatment. The warning was added as an outcome of the periodic safety update assessment concluded on 27 June 2017.(1)

The MHRA has informed health professionals in the U.K. of the update to the product information of denosumab. In December 2015 the MHRA had published a Drug Safety Update article about very rare reports of osteonecrosis of the external auditory canal with bisphosphonates, which are – like denosumab – known to be associated with osteonecrosis of the jaw. For all these medicines, the risk of osteonecrosis at other sites of the body continues to be kept under close review.(2)

Gabapentin: Respiratory depression without concomitant opioid use
Ireland – The HPRA has warned health professionals that in rare cases gabapentin can cause severe respiratory depression even without concomitant opioid use. Dosage adjustments should be considered, especially in patients with risk factors such as the use of CNS depressant medication, compromised breathing function,
respiratory or neurological disease, renal impairment and age.\(^{(1)}\)

The warning follows a review by the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC), which recommended that the product information for gabapentin should be updated to reflect this risk.\(^{(2)}\)

\[\textbf{Hydroxocobalalmine antidote kit: Acute kidney injury}\]

\textbf{Japan} – The PMDA has reviewed information related to reports of acute kidney injury reported in patients receiving hydroxocobalamin as treatment for cyanogen and cyanide poisoning both in Japan and overseas. Cases of renal tubular necrosis have also been reported. The MHLW has recommended an update to the product information for the hydroxocobalamin kit (Cyanokit\textsuperscript{®}), advising health professionals to monitor patients carefully for signs of this adverse event.

\[\textbf{Diagnostics}\]

\textbf{Hightop HIV home testing kits: Unreliable results}\]

\textbf{United Kingdom} – The MHRA has informed the public that it has seized more than 100 unreliable HIV home-testing kits and is investigating a number of kits that may be unreliable and may provide false results. The affected kit is the Hightop HIV/AIDS Home Test Kit. The kits, manufactured by Qingdao Hightop Biotech Co Ltd, do not have a valid CE mark, meaning that the product has not undergone the regulatory assessments required for the EU market. All sales of the product into the U.K. market have been stopped by the manufacturer.

\[\textbf{Known risks}\]

\textbf{Warfarin: Calciphylaxis}\]

\textbf{Japan} – The MHLW, upon advice from the PMDA, has required updates to the product information for warfarin to warn about the risk of calciphylaxis.\(^{(1)}\)

In the EU, product information for warfarin was amended in 2016 to include a warning about this risk. Calciphylaxis is a very rare but serious condition that causes vascular calcification and cutaneous necrosis, and is most commonly observed in patients with known risk factors such as end-stage renal disease. Cases have been reported in patients taking warfarin, including those with normal renal function, and evidence suggests that on rare occasions warfarin use might lead to calciphylaxis. If calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin.\(^{(2, 3)}\)

\[\textbf{Local corticosteroids: Central serous chorioretinopathy}\]

\textbf{United Kingdom} – The MHRA has advised health professionals that patients treated with both systemic or local corticosteroids...
should be asked to report any blurred vision or other visual disturbances. Referral to an ophthalmologist should be considered to establish the cause of the vision problems.

Treatment with systemic corticosteroids is a known risk factor for central serous chorioretinopathy (CSCR), an accumulation of subretinal fluid that can ultimately cause retinal detachment. CSCR has also been listed as a rare side effect with all locally administered corticosteroid formulations. Although the causes of blurred vision are various, CSCR should be considered as a possible cause in patients treated with corticosteroids, including those administered through local routes.

► Drug Safety Update volume 11 issue 1, August 2017: 2.

**Hydroquinone skin lighteners:**
**Skin damage; environmental damage**
Canada – Health Canada will be changing the prescription status of skin-lightening products containing hydroquinone at concentrations greater than 2%. These products will be available by prescription only as of August 2018, due to their risks for the skin and for the environment. A transition plan was developed following an online consultation with stakeholders.

Skin lighteners containing more than 2% hydroquinone can cause severe skin redness, burning or stinging, dryness or cracking of the skin, blisters or oozing, or skin discolouration. They can also cause cancer in laboratory animals, and potentially in humans.


**Review outcomes**

**E. coli probiotic:**
**Use in irritable bowel syndrome only**
European Union – At the request of the German regulatory authority the EMA has reviewed a probiotic containing *Escherichia coli* bacteria (Symbioflor 2® and associated names) and has concluded that it can continue to be used for irritable bowel syndrome in adults. Benefit has not yet been established in children. The medicine should no longer be used for other functional gastrointestinal disorders as there are insufficient data to support this use.

The product information will be updated in line with this review. The marketing authorization holder has been requested to submit results of a well-designed study to national authorities demonstrating the medicine’s efficacy safety for treating different variants of irritable bowel syndrome, as a condition for continued marketing.

► EMA Press release, 23 June 2017.
EMA Article 31 referrals. Symbioflor 2.

**Modified-release paracetamol:**
**To be removed from market**
European Union – The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the marketing authorizations of modified-or prolonged-release release paracetamol should be suspended. The decision was taken in view of the difficulties of managing overdose in patients.

Although modified-release paracetamol tablets have acceptable benefits and risks when used in the approved way, experience has shown that in overdose the treatment procedures – which were developed for
immediate-release paracetamol – are not appropriate.
► EMA News, 1 September 2017.

**Gadolinium-based contrast agents: Restrictions maintained**

**European Union** – The EMA has confirmed its recommendations to restrict the use of some intravenous linear gadolinium agents used in MRI body scans and to suspend the authorizations of others. Macrocyclic gadolinium agents can continue to be used, but only at the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable.

**Australia** – The TGA has reviewed recent information on gadolinium-based contrast agents and is working with marketing authorization holders to update the relevant product information. Health professionals were advised to use gadolinium-based contrast agents only where necessary, to use the lowest effective dose, to carefully consider the choice of agent, and to avoid repetitive scans using these contrast agents unless deemed clinically necessary.

**New Zealand** – Medsafe and its Medicines Adverse Reactions Committee (MARC) considered that use of gadolinium based contrast agents should be restricted to situations where they are expected to provide additional information allowing the patient's condition to be diagnosed or monitored correctly.
► Medsafe Alert communication, 21 August 2017.

**Non-compliance with good practices**

**Dr Reddy’s Laboratories**

German regulators have issued a statement of non-compliance with good manufacturing practices (GMP) for Dr. Reddy’s Laboratories Ltd’s manufacturing site located in Qutubullapur Mandal, Ranga Reddy District, Bachupally Village. In an inspection conducted on 1st August 2017 critical deficiencies were observed including systematic invalidation of out-of-specification results in hundreds of cases, the systematic failure of systems to document and report discrepancies, non-conformances, incidents and unusual events, and false confirmation of successful cleaning of rooms and equipment.

The German regulators issued a rapid alert concerning the products on the German market and proposed an EU-wide import stop until successful re-inspection of the site.

**Hetero Labs Limited**

The FDA has issued a warning letter to Hetero Labs Limited over non-compliance with GMP at its Unit V facility at Polepally Village, Jadcherla Mandal in Telangana, India. This follows an inspection of the site conducted on 7-16 December 2016, during which deficiencies were observed with regard to investigation of out-of-specification testing results, cleaning, written procedures for quality control, and in-process controls. The company has been given 15 days to respond, specifying the corrective actions taken to remedy the shortcomings and prevent their recurrence.
Quinine sulfate (Africa)
The WHO Medical Product Alert No. 2/2017 relates to the circulation of two confirmed falsified versions of quinine sulfate in the Democratic Republic of the Congo. The two products contain zero active pharmaceutical ingredient.

Quinine sulphate is used for the treatment of P. falciparum malaria in the region. In April 2017, a local non-governmental organization (NGO) discovered the falsified products in pharmacies in the north-east of the Democratic Republic of the Congo. The products were submitted to a WHO-prequalified laboratory for testing. The analysis showed that neither of the two products contained any of the stated active pharmaceutical ingredient. The details on the product labels are shown below.

<table>
<thead>
<tr>
<th>Product 1</th>
<th>Product 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product name:</strong> Quinine sulphate 300</td>
<td>Quinine bisulphate 300mg. B.P.</td>
</tr>
<tr>
<td><strong>Batch number:</strong> 15946</td>
<td>7422</td>
</tr>
<tr>
<td><strong>Expiry date:</strong> 03/18</td>
<td>12-2018</td>
</tr>
<tr>
<td><strong>Manufacturing date:</strong> 02/15</td>
<td>5-2015</td>
</tr>
<tr>
<td><strong>Manufacturer name stated on the label:</strong> Remedica</td>
<td>Laboratory &amp; Allied Ltd</td>
</tr>
</tbody>
</table>

The manufacturers indicated on the label of the two products, Remedica and Laboratory & Allied Ltd, have stated that they did not manufacture these specific products. The product details shown above do not correspond to the genuine manufacturer records.

► WHO Medical Product Alert No. 2/2017 (includes photographs).

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

Cancer medicines (East Africa)
The WHO Medical Product Alert No. 3/2017 relates to falsified Avastin (bevacizumab) and Sutent (sunitinib malate) circulating in East Africa. The two falsified medicines were discovered and seized by the National Drug Authority of Uganda in July 2017 and reported to WHO. Both products were being distributed in the vicinity of various cancer treatment centres in Kampala, Uganda.

The genuine manufacturers of both products have confirmed that they did not manufacture these products. Avastin* is the trade name of a medicine manufactured by Roche/Genentech for the treatment of various cancers. Sutent* is the trade name of a
medicine for the treatment of pancreatic cancer manufactured by Pfizer. Neither of the two products is manufactured by AstraZeneca as shown on the falsified versions.

These falsified versions of Avastin® and Sutent® are being presented in plastic bottles containing blue/grey tablets. The genuine version of Avastin® is supplied only as an injection for intravenous use. Genuine Sutent® is only available as gelatin capsules.

Details of the falsified products are as follows:

<table>
<thead>
<tr>
<th>Product 1</th>
<th>Product 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product name:</td>
<td>Avastin</td>
</tr>
<tr>
<td>Batch number:</td>
<td></td>
</tr>
<tr>
<td>Expiry date:</td>
<td></td>
</tr>
<tr>
<td>Manufacturer name stated on the label:</td>
<td>Astrazeneca and AstraZeneca</td>
</tr>
</tbody>
</table>

► WHO Medical Product Alert No. 3/2017. (includes photographs)

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

**Counterfeit packs of schizophrenia medicine (Germany, Denmark)**

German and Danish parallel importers and the Danish Medicines Agency have withdrawn a total of four batches of the schizophrenia medicine paliperidone palmitate (Xeplion®) 150 mg from wholesale distributors, hospitals and pharmacies, because the batches contained counterfeit packs.

An analysis of the counterfeit packs from two of the affected batches by the manufacturer of the genuine product, Janssen, has shown that the outer packaging has been falsified, but the syringe and its content as well as the enclosed needles are authentic products from Janssen, and no signs were found that syringes and needles have been tampered with. The Danish Medicines Agency therefore considers that the risk for patients is low.

However, it cannot be ruled out that the counterfeit packs have been handled improperly since they were packed and handled outside the legal chain. A risk of falsification has been identified in additional batches, which have been quarantined. The Danish Medicines Agency continues to investigate the matter in collaboration with the European Medicines Agency and the regulators of the other affected countries.

Regulatory news

Pre-market assessment

Strategic approach to development of children’s medicine
European Union, United States of America

The EMA and the U.S. FDA have finalized their joint proposal to promote the use of innovative approaches in the development of medicines for Gaucher disease. The proposed strategies can apply to medicines development for rare diseases in children in general.

The strategy document encourages medicine developers to make better use of extrapolation of available clinical data from adults to children through modelling and simulation, and to conduct multi-arm, multi-company clinical trials on several new medicines at the same time, with the same control arm serving more than one medicine under evaluation. The overall aim is to reduce the number of patients in clinical trials while maintaining high quality standards, thus reducing the burden on children and their families.


Generic products in the U.S.
United States of America

The FDA has taken two steps to expedite market entry of needed generic medicines. These actions are among the first taken under the Agency’s Drug Competition Action Plan announced in late May.

Firstly, to encourage generic drug development, the FDA posted a list of branded drugs that have no listed patents or exclusivities and for which the agency has yet to approve an Abbreviated New Drug Application (ANDA). The Agency intends to expedite the review of generics on this list, which will be refined and updated periodically.

Secondly, the FDA has announced a change to its policy on prioritizing the review of needed generics. The review of applications for a given medicine will be expedited until there are three FDA-approved generics for that medicine. This policy change is based on data indicating that significant price reductions occur when there are multiple FDA-approved generics available.


Revised EMA clinical trial guidelines
European Union

The EMA has released its revised guidelines for first-in-human clinical trials. The revision takes into account the increasing complexity of trial protocols. It provides guidance on the calculation of the starting dose, subsequent dose escalations and criteria for the maximum dose. Guidance is also provided on criteria to stop a study, the rolling review of emerging data especially regarding safety, and the handling of adverse events in relation to stopping a trial or progressing to the next dosing level.


Joint EU assessment platform
European Union

The EMA and the European Network for Health Technology Assessment (EUnetHTA) have launched a new joint platform that will facilitate
alignment of data requirements with evidence being generated for both regulators as well as the bodies that provide recommendations to payers and other decision-makers.

The platform will enable medicine developers to obtain simultaneous, coordinated advice and health technology assessment bodies. Patient representatives will be involved in parallel consultations on a routine basis. The improved consultation, coordination and streamlined logistics are expected to lead to more robust outcomes.


**Emergency importation list**

Canada – Health Canada has published an initial list of medicines for which there is an urgent public health need, and which are authorized for sale in the U.S., the EU or Switzerland, but not yet in Canada. Health Canada will permit these drugs to be imported for use in Canada. Provisions are in place for reporting of adverse reactions and organizing recalls.

The initial list includes medicines to treat opioid use disorder and tuberculosis. Medicines will remain on the list for one year, renewable if there is a continued need for access. Additional medicines may be added to the list in the future, for example to treat pandemic viruses or to address other public and military health emergencies.


**Standardized testing panel for Zika**

United States of America – The FDA has made available a panel of human plasma samples to aid in the regulatory evaluation of serological tests to detect recent Zika virus infection.

The sample panel consists of plasma samples from anonymous individuals infected with Zika, West Nile, or dengue viruses. Although the panel is not for research purposes, diagnostic developers can use these samples to assess whether their tests can help distinguish recent Zika virus infection from infection with West Nile or dengue viruses. Using the same serological panel to evaluate different devices available under Emergency Use Authorization (EUA) will help public health professionals compare the performance of different Zika virus tests. The FDA panel is available to developers who have interacted with the Agency through the pre-EUA process and have devices that are in the final stages of validation. Other developers interested in requesting a panel may contact the Agency.


**Post-market monitoring**

**EMA platform gains trade mark**

European Union – The EU Intellectual Property Office (EUIPO) has approved the registration of the name “EU PAS Register” as a European Union trade mark.

The EU electronic Register of Post-Authorisation Studies (EU PAS Register) was developed through the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), which is coordinated by EMA. Launched in November 2010, this openly accessible platform currently includes information on more than 1 100 observational post-authorization studies, of which about a third are finalized. The trade mark will reinforce the EMA’s legal control over the name of the platform and its content.

Automated FDA field alert reports
United States of America – After the successful completion of a four-year pilot phase, the FDA has released a new version of its automated Form FDA 3331a for electronic submission of field alert reports for pharmaceutical products. The new form does not require signatures, requires no additional software or licenses beyond Adobe Acrobat Reader and an email client, and enables the FDA to import data directly to its systems.

Field alert reports enable the regulators to quickly identify quality defects in distributed products that may present a potential safety threat. The Agency is working on the technical requirements for receiving field alert reports as part of the electronic Common Technical Document (eCTD) through the electronic submissions gateway.
➤ FDA Notice to Industry, 15 June 2017.

GMP compliance
Indian manufacturers to submit self-certification
India – The Drugs Controller General of India has issued a notice requesting pharmaceutical manufacturers to submit their self-assessment reports and self-certification of compliance with good manufacturing practice (GMP) and good laboratory practice (GLP) requirements to the State Licensing Authorities and to the Central Drugs Standard Control Organization (CDSCO) by 30 August 2017. The notice states that issues related to the possibility of self-certification, followed by third-party certification and detailed audit, have been deliberated at the highest level.

An earlier notice requesting mandatory self-audits and submission of self-assessment reports had been issued in July 2015, and CDSCO had provided companies with a checklist of GMP and GLP requirements as specified under Schedule M and Schedule L-1 of the Drugs and Cosmetics Act and Rules of India. However, CDSCO is yet to receive self-inspection reports from manufacturers.

Collaboration
China Food and Drug Administration joins ICH
Montreal – At its meeting held in Montreal, Canada on 27 May to 1 June 2017, the Assembly of the The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) approved the China Food and Drug Administration (CFDA) as a new Regulatory Member, and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as a new Observer. With these new parties, ICH now has 14 members and 23 observers. Full details are available on the ICH website1.

At the meeting the ICH Assembly also agreed to begin work on two new topics: a harmonized guideline on the use of extrapolation in children’s medicine development, and revised general considerations for clinical trials. The Assembly further adopted new guidance documents and made some revisions to its Articles of Association and rules of procedure to keep operations streamlined with a growing number of members and observers.
➤ ICH Press release, 19 June 2017.

1 http://www.ich.org/about/membership.html
U.S.-EU cooperation in inspections
The European Commission (EC), the U.S. FDA and the EMA have signed a new confidentiality commitment that allows the US regulator to share non-public and commercially confidential information – including trade secret information relating to medicine inspections – with EU regulators. This confidentiality commitment is a milestone in the ongoing implementation of the mutual recognition of inspections of medicine manufacturing sites.

The EU and the U.S. have had confidentiality arrangements in place since 2003, allowing for the exchange of confidential information as part of their regulatory and scientific processes. However, complete exchange of information was not possible under these arrangements. The new confidentiality commitment formally recognises that FDA’s EU counterparts have the authority and demonstrated ability to protect the relevant information. This step will now allow the sharing of full inspection reports, allowing regulators to make decisions based on findings in each other’s inspection reports and to make better use of their inspection resources to focus on manufacturing sites of higher risk.

IGDRP, IPRF initiatives to join
Montreal – The International Generic Drug Regulators Programme (IGDRP) and the International Pharmaceutical Regulators Forum (IPRF) have agreed to consolidate their collaborative initiatives. The decision was taken at the 5th IGDRP meeting, held in Montreal, Canada, on 5–8 June 2017. The joint initiative will be operational in January 2018; the first face-to-face meeting of the consolidated management committee is planned for June 2018.

The agreement follows an in-depth review of various governance models. The consolidation is expected to realize several opportunities, including: enabling a shared vision for information exchange and regulatory cooperation; maximising synergies and avoiding duplication of effort; creating a regulatory hub for pharmaceuticals that covers all medicinal products, enabling closer linkages with initiatives to simplify the numerous forms of international regulatory collaboration; and improving governance for the management committees and technical working groups.

Medicines labels
Improved labelling in Australia
Australia – The TGA has introduced improvements to help align medicine labels with international best practice. The changes will be implemented over a four-year period. Under the new rules, the names of active ingredients will be updated to be in line with nonproprietary names used internationally, and medicines names will be displayed more prominently on the labels. Critical information will be displayed in a standardized manner and will include mandatory declaration of some additional allergens. The changes will also provide for easier dispensing.
Under discussion

European Union – Comments are invited to an EMA reflection paper on aspects to consider in development of medicines for older people. Comments are particularly invited on the accuracy of tablet breaking, the administration of medicines through feeding tubes, and on multiple compliance aids and drug dispensing systems.

► EMA News, 1 August 2017.
Closing date: 31 January 2018.

European Union – The EMA has released for public consultation a concept paper on the development and lifecycle of personalized medicines and companion diagnostics that allow identifying patients who are most likely to benefit from a specific medicine, and those likely to be at increased risk of serious adverse reactions. Recently revised EU legislation foresees cooperation between medicines regulators and EU notified bodies, which conduct the conformity assessment of diagnostics in the EU.

Closing date: 15 November 2017.

European Union – A concept on the non-clinical development of radiopharmaceuticals has been released for public comment on the EMA website. The draft guidance complements existing guidelines, and applies to radiodiagnostics as well as radiotherapeutics. It will focus on targeted non-clinical programmes for specific development settings and product types. The paper is not intended to duplicate guidance on dosimetry.

► EMA Consultation, 1 August 2017.
Closing date: 31 October 2017.

European Union – The EMA has launched a public consultation on its proposed recommendations on how best to use aminoglycoside antibiotics in animals to reduce the risk of antimicrobial resistance. (1) WHO has classified aminoglycosides as critically important for human health. Comments have also been invited on a draft reflection paper regarding the off-label use of veterinary antimicrobials, which contributes to the risk of resistance. (2)

Closing date: 31 October 2017 /
Closing date: 31 January 2018

European Union – The EMA has proposed revised guidelines on pharmacovigilance for medicines used in children and adolescents up to 18 years of age. The revision takes into account the improved situation with regard to off-label use, and considers medicine-related risks in the context of school and sports performance, alcohol and nicotine consumption and possible diversion of medicines to friends. The revised guidance should also be of interest to non-regulatory groups such as parents, caregivers and healthcare professionals.

► EMA Consultation, 2 August 2017.
Closing date: 13 October 2017.

European Union – The EMA has released a concept paper on revision of its guideline on clinical development of vaccines. The revision of the current guideline is proposed to incorporate lessons learned in clinical development of new and improved vaccines since 2007, as well as aspects of developing
Under discussion

vaccines administered during pregnancy with the main or sole intent of providing a benefit to the unborn child.

► EMA Consultation, 23 June 2017.
   Closing date: 30 September 2017.

Ireland – The Minister for Health of Ireland has announced the opening of a public consultation on biosimilar medicines. The consultation will inform the development of Ireland’s first National Biosimilar Medicines Policy, with the aim of increasing the use of these more cost-effective medicines in Ireland.

   Consultation closing date: 22 September 2017.

Australia – The TGA is seeking comments on proposed options on whether there is a need in Australia for additional naming requirements for biological medicines as a way of strengthening traceability and pharmacovigilance.

► TGA Consultation, 28 July 2017.
   Closing date: 8 September 2017.

Geneva – WHO has sought comments on its pilot procedure for WHO prequalification of similar biotherapeutic products. This pilot project is a step towards making some of the most expensive treatments for cancer more widely available. The first invitation for expression of interest to prequalify rituximab-and trastuzumab-containing products is planned to be published in October 2017.

   Closing date: 16 August 2017.

Canada – Health Canada has opened a consultation on proposed changes to regulations that would make it mandatory for certain health care institutions to report serious adverse drug reactions and medical device incidents.

► Health Canada Consultation, 28 June 2017.
   Closing date: 11 August 2017.

India – The Office of the Drug Controller General of India has published a notice listing some of the steps taken in the past to streamline regulatory procedures, and has asked industry to provide feedback on other proposed approaches that would allow to streamline the regulatory process further.

► CDSCO Notice, 27 June 2017.
   Closing date: 31 July 2017.

India – The Central Drugs Standard Control Organisation of India has published a draft standard operating procedure for declaring a sample as being of substandard quality.

► CDSCO Notice, 27 June 2017.
   Closing date: 31 July 2017.

SOP for handling of Not of Standard Quality (NSQ) drugs samples. Draft.

Australia – The TGA has published feedback on its proposed criteria to identify comparable overseas regulators (CORs) as providers of assessment reports and possible work-sharing partners in the assessment of medicine registration applications. A final guideline is expected to be published in December 2017.

**Approved**

**L-glutamine for sickle cell disease**  
**Product name:** Endari®  
**Dosage form:** Oral powder  
**Class:** Amino acid  
**Approval:** FDA (orphan drug designation)  
**Use:** To reduce the acute complications of sickle cell disease in adults and children 5 years of age and older  
**Benefits:** Fewer and shorter hospital visits for sickle cell crises, fewer occurrences of acute chest syndrome than with placebo.  
**Notes:** Only one other medicine is approved in the U.S. for sickle cell disease.  
► FDA News release, 7 July 2017.

**Betrixaban to prevent venous thromboembolism in certain patients**  
**Product name:** BevyxXa®  
**Dosage form:** Capsules  
**Class:** Anticoagulant, Factor Xa inhibitor  
**Approval:** FDA  
**Use:** Prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications  
**Benefits:** In a clinical trial, betrixaban was more efficacious than enoxaparin in preventing thrombotic events.  
**Safety information:** Patients treated with betrixaban who are receiving neuraxial anaesthesia or undergoing spinal puncture are at risk of spinal/epidural haematoma. The risk may be increased by the use of in-dwelling epidural catheters or the concomitant use of medical products affecting haemostasis. These haematomas may result in long-term or permanent paralysis.  
► Prescribing information for BevyxXa®, revised 6/2017.

**Meropenem and vaborbactam for complicated urinary tract infection**  
**Product name:** Vabomere®  
**Dosage form:** Sterile powder for injection for intravenous use  
**Class:** Combination of a penem antibacterial (meropenem) and a beta-lactamase inhibitor (vaborbactam)  
**Approval:** FDA (priority review, qualified infectious disease product (QIDP) designation)  
**Use:** Treatment of adults with complicated urinary tract infections (cUTI). To reduce the risk of drug-resistance, the product should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.  
**Benefits:** Additional treatment option for cUTI  
**Safety information:** This product can cause allergic reactions and seizures. It should not be used in patients with a history of anaphylaxis in response to beta-lactams  

**C1 esterase inhibitor (human) to prevent hereditary angioedema**  
**Product name:** Haegarda®  
**Dosage form:** Lyophilized concentrate for subcutaneous injection  
**Class:** C1-esterase inhibitor (C1-INH)  
**Approval:** FDA (orphan drug designation)  
**Use:** Prevention of hereditary angioedema attacks in adolescent and adult patients  
**Benefits:** Reduced number of attacks, compared to placebo.  
**Notes:** Hereditary angioedema causes attacks of rapid swelling of the hands, feet, limbs, face, intestinal tract or airway. These attacks can occur spontaneously, or can be triggered by stress, surgery or infection. The product is not suitable to treat acute attacks.  
► FDA News release, 22 June 2017.

**Delafloxacin for acute bacterial skin infections**  
**Product name:** Baxdela®  
**Dosage form:** Tablets; injection for intravenous use  
**Class:** Fluoroquinolone antibiotic  
**Approval:** FDA
Approved

**Use:** Treatment of acute bacterial skin and skin structure infections caused by designated susceptible bacteria. Delafloxacin should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

**Benefits:** No less effective than a combination of vancomycin and aztreonam in two multicentre clinical trials.

**Safety information:** Like other fluoroquinolones delafloxacin is associated with: (1) a risk of disabling and potentially irreversible serious adverse reactions that can occurred together, including tendinitis and tendon rupture, peripheral neuropathy and central nervous system effects; and (2) a risk of exacerbation of myasthenia gravis.

► Prescribing information for Baxdela®, revised 6/2017.

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**Glecaprevir and pibrentasvir for hepatitis C**

**Product name:** EU: Maviret®; U.S.: Mavyret®

**Dosage form:** Film-coated tablets

**Class:** Fixed-dose combination of two direct-acting antivirals, a HCV NS3/4A protease inhibitor (glecaprevir), and HCV NS5A inhibitor (pibrentasvir)

**Approval:** EMA (accelerated approval); FDA (priority review, breakthrough therapy)

**Use:** Treatment of chronic hepatitis C virus (HCV) infection in adults

**Benefits:** Highly effective against all genotypes of HCV. Can be used in patients with severe renal impairment, including in those on dialysis.

► EMA Press release, 23 June 2017.


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**Sofosbuvir, velpatasvir and voxilaprevir for hepatitis C**

**Product name:** Vosevi®

**Dosage form:** Film-coated tablets

**Class:** Fixed-dose combination of three direct antivirals: a nucleotide analogue non-structural protein NS5B polymerase inhibitor (sofosbuvir), an HCV NS5A inhibitor (velpatasvir) and a novel pan-genotypic HCV NS3/4A protease inhibitor (voxilaprevir).

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

**Use:** Treatment of adult patients with newly diagnosed therapy-related AML, or AML with myelodysplasia-related changes

**Benefits:** Longer overall survival than with separate treatments of daunorubicin and cytarabine.

**Safety information:** The product has been associated with serious or fatal bleeding events. This product should not be interchanged

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**Cladribine for relapsing multiple sclerosis**

**Product name:** Mavenclad ®

**Dosage form:** Tablets

**Class:** Antimetabolite; **ATC code:** L01BB04

**Approval:** EMA

**Use:** Treatment of adult patients with highly active relapsing multiple sclerosis as defined by clinical or imaging features.

**Benefits:** Ability to reduce the frequency of relapses and to delay disease progression

**Safety information:** Cladribine can cause lymphopenia, which can be severe and long-lasting, and infections including herpes zoster.

► EMA/CHMP Summary of opinion, 22 June 2017.

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**Daunorubicin and cytarabine for two types of acute myeloid leukaemia (AML)**

**Product name:** Vyxeos®

**Dosage form:** Liposome for injection for intravenous use

**Class:** Fixed-dose combination of an anthracycline topoisomerase inhibitor (daunorubicin) and a nucleoside metabolic inhibitor (cytarabine)

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

**Use:** Treatment of adult patients with newly diagnosed therapy-related AML, or AML with myelodysplasia-related changes

**Benefits:** Longer overall survival than with separate treatments of daunorubicin and cytarabine.

**Safety information:** The product has been associated with serious or fatal bleeding events. This product should not be interchanged
with other daunorubicin- and/or cytarabine-containing products.  

**Note:** This is the first FDA-approved treatment specifically for patients with either of these two types of high-risk AML.


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**Gemtuzumab ozogamicin for acute myeloid leukaemia (AML)**  
**Product name:** Mylotarg®  
**Dosage form:** Lyophilized cake or powder for injection  
**Class:** CD33-directed antibody-drug conjugate  
**Approval:** FDA (orphan drug designation)  
**Use:** Treatment of adults with newly diagnosed CD33-positive AML; treatment of patients aged 2 years and older with relapsed or refractory CD33-positive AML.  
**Benefits:** Longer event-free survival period than with chemotherapy alone; longer median overall survival than with best supportive care.  
**Safety information:** Severe side effects include liver damage, hepatic veno-occlusive disease, low blood counts, infections, infusion-related reactions and severe bleeding.  
**Notes:** (1) Mylotarg® was originally received accelerated FDA-approval in May 2000 as a stand-alone treatment for older patients with CD33-positive AML who had experienced a relapse. The product was voluntarily withdrawn from the market after subsequent confirmatory trials failed to verify clinical benefit and demonstrated safety concerns, including a high number of early deaths. The 2017 approval includes a lower recommended dose, a different schedule in combination with chemotherapy or on its own, and a new patient population.  

► FDA News release, 1 September 2017.

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**Enasidenib for certain types of AML**  
**Product name:** Idhifa®  
**Dosage form:** Tablets  
**Class:** Isocitrate dehydrogenase-2 inhibitor  
**Approval:** FDA (priority review; orphan drug designation)  
**Use:** Treatment of adult patients with relapsed or refractory acute myeloid leukaemia (AML) who have a specific genetic mutation  
**Benefits:** Ability to achieve complete remission in some patients and a reduction in the need for both red cell and platelet transfusions lasting several months.  
**Safety information:** An adverse reaction known as differentiation syndrome can occur and can be fatal if not treated. If differentiation syndrome is suspected, patients should be treated with corticosteroids and closely monitored until symptoms resolve.  
**Note:** The product is approved for use with a companion diagnostic, the RealTime IDH2 Assay, which is used to detect specific mutations in patients’ IDH2 gene.  

► FDA News release, 1 August 2017.

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**Neratinib to reduce risk of breast cancer**  
**Product name:** Nerlynx®  
**Dosage form:** Tablets  
**Class:** Kinase inhibitor  
**Approval:** FDA  
**Use:** For the extended adjuvant treatment of early-stage, HER2-positive breast cancer in adult patients previously treated with trastuzumab  
**Benefits:** Reduced risk of breast cancer recurrence  
**Safety information:** Severe potential adverse effects include diarrhoea and liver damage. Patients should be given loperamide for the first 56 days of treatment and as needed thereafter, together with additional antidiarrheals, fluids and electrolytes as clinically indicated to help manage diarrhoea. Neratinib may cause harm to a developing foetus or a newborn child.  


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**Tivozanib for kidney cancer**  
**Product name:** Fotivda®  
**Dosage form:** Hard capsules  
**Class:** Protein kinase inhibitor;  
**ATC code:** L01XE34  
**Approval:** EMA  
**Use:** First line-treatment of adult patients with advanced renal cell carcinoma (RCC) and treatment of certain adult patients following
Approved

disease progression after one prior cytokine therapy for advanced RCC.

**Benefits**: Ability to improve progression-free survival in patients with advanced disease

► EMA/CHMP Summary of opinion, 22 June 2017.

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**Guselkumab for plaque psoriasis**

**Product name**: Tremfya®

**Dosage form**: Subcutaneous injection

**Class**: Interleukin-23 blocker;

**ATC code (temporary)**: L04AC16

**Approval**: FDA

**Use**: Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

**Benefits**: Additional treatment option for psoriasis.

**Safety information**: Guselkumab may increase the risk of infection. Patients should be evaluated for tuberculosis before starting treatment

► FDA prescribing information for Tremfya®; revised July 2017.

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**Benznidazole for Chagas disease**

**Dosage form**: Oral tablets

**Class**: Nitroimidazole derivative;

**ATC code**: P01CA02

**Approval**: FDA (accelerated approval, priority review; orphan product designation)

**Use**: Treatment of children aged 2 to 12 years with Chagas disease

**Benefits**: Significantly more seroconversions from positive to negative antibody test compared with placebo.

**Safety information**: Benznidazole can cause serious skin reactions, nervous system effects and bone marrow depression. Based on findings from animal studies, benznidazole could cause foetal harm.

**Notes**: Chagas disease is a parasitic infection that can cause serious heart illness and can affect swallowing and digestion in the long term. This is the first FDA-approved treatment for Chagas disease.


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**Ciclosporin paediatric eye drops for rare eye allergy in children**

**Product name**: Verkazia®

**Dosage form**: Eye drops

**Class**: Immunosuppressant;

**ATC code**: S01XA18

**Approval**: EMA (orphan designation; accelerated assessment)

**Use**: Treatment of severe vernal keratoconjunctivitis in children from 4 years of age and adolescents

**Benefits**: Ability to improve ocular surface damage and reduce symptoms of severe vernal keratoconjunctivitis in children and adolescent patients.


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**Lutetium oxodotreotide for certain gastroenteric cancers**

**Product name**: Lutathera®

**Dosage form**: Solution for infusion

**Class**: Radiolabelled peptide targeting subtype 2 somatostatin (sst2) receptors;

**ATC code**: V10XX04

**Approval**: EMA (orphan designation)

**Use**: Treatment of gastro-entero-pancreatic neuroendocrine tumours

**Benefits**: Ability to improve progression-free survival compared with octreotide long-acting release (LAR), a somatostatin receptor agonist, in patients with certain types of tumours.


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**Gene cell therapy**

**Tisagenlecleucel for certain leukaemias**

**Product name**: Kymriah®

**Dosage form**: Autologous CAR T cells for infusion

**Class**: Genetically-modified autologous T-cell immunotherapy. chimeric antigen receptor (CAR) designed to kill B-cells with a C19 surface antigen.

**Approval**: FDA (fast track, priority review and breakthrough therapy designations)

**Use**: Treatment of children and young adults up to 25 years of age with B-cell precursor acute lymphoblastic leukaemia (ALL) that is refractory or in second or later relapse.
Benefits: Remission rate of 83% within three months in a clinical trial.

Safety information: The product carries a boxed warning about the risk of cytokine release syndrome (CRS), which causes high fever and flu-like symptoms, and the risk of neurological events. Both these events can be life-threatening. Other severe side effects of Kymriah include serious infections, hypotension, acute kidney injury, fever, and hypoxia. Most symptoms appear within one to 22 days following infusion.

Note: This is the first gene therapy available in the United States.


Biosimilars

Bevacizumab

Product name: Mvasi® (bevacizumab-awwb)
Reference product: Avastin®
Approval: FDA
Use: Treatment of adult patients with certain colorectal, lung, brain, kidney and cervical cancers.

Safety information: Like Avastin®, Mvasi® carries a Boxed Warning about an increased risk of gastrointestinal perforations; surgery and wound healing complications; and severe or fatal pulmonary, gastrointestinal, central nervous system and vaginal bleeding.

Note: Bevacizumab-awwb is the first biosimilar approved in the U.S. for the treatment of cancer.


Adalimumab

(1)

Product name: Imraldi®
Reference product: Humira®
Approval: EMA
Use: Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriatic plaque psoriasis, hidradenitis suppurativa, Crohn's disease, paediatric Crohn's disease, ulcerative colitis and uveitis.

EMA/CHMP Summary of opinion, 22 June 2017.

(2)

Product name: Cyltezo®
Reference product: Humira®
Approval: FDA
Use: Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis and plaque psoriasis.


Early access

Idebenone for Duchenne’s muscular dystrophy

Product name: Raxone®
Dosage form: Tablets
Class: Antioxidant
Approval: MHRA Early Access to Medicines Scheme (EAMS)
Use: Treatment of patients aged 10 years and older with Duchenne's muscular dystrophy not currently taking glucocorticoids and showing clear signs of deteriorating lung function.

Benefits: Ability to slow the decline of respiratory function

Note: The product is licensed in the U.K. for the treatment of Leber's hereditary optic neuropathy, a rare eye condition.

MHRA Public assessment report.

Extensions of indications

Ibrutinib for graft-versus-host disease

Product name: Imbruvica®
Approval: FDA (priority review, breakthrough therapy; orphan drug designation)
Newly approved use: Treatment of chronic graft-versus-host disease (cGVHD)
Note: cGVHD is a serious and life-threatening condition that may occur in patients with blood cancer who receive a stem cell transplant. This is the first FDA-approved therapy for cGVHD.

Publications and events

Research and development

**Call for checks on clinical trials**

Amsterdam – The Netherlands-based Wemos Foundation has published a summary of reports about clinical trials from four African countries. The findings show that the trials were not always conducted according to ethical guidelines, putting the trial participants at risk of being harmed or having their rights violated. For example, some clinical trial participants were not well informed that they were signing up for a trial, and others agreed to participate because it was the only way for them to get treatment in their country. In case of physical harm, receiving financial compensation was shown to be extremely difficult. The report recommends that EMA should perform more checks on clinical trials conducted in low- and middle-income countries and should make its research reports and its good clinical practice (GCP) inspection reports public. (1)

In April 2017 the European Parliament had reminded EMA of its commitment to perform extra checks on clinical trials carried out outside the European Union before granting market authorization. (2)


(2) European Parliament resolution of 27 April 2017 with observations forming an integral part of the decision on discharge in respect of the implementation of the budget of the European Medicines Agency for the financial year 2015 (2016/2169(DEC)). Point 18.

**Clinical evidence: beyond RCTs**

Randomized, controlled trials (RCTs) have long been presumed to be the ideal source of data on the effects of treatment. However, other methods of obtaining evidence for decisive action are receiving increased interest, prompting new approaches to leverage the strengths and overcome the limitations of different data sources. A new review article describes the use of RCTs and alternative data sources from the vantage point of public health, illustrates key limitations of RCTs, and suggests ways to improve the use of multiple data sources for health decision making.


Access to medicines

**Access to cancer care**

Amsterdam – The Access to Medicine Foundation has published an analysis of industry activities that aim to improve access to cancer care in low- and middle-income countries. This is the first landscape analysis of pharmaceutical companies’ actions to address cancer care in low- and middle-income countries. In its study, the Foundation describes and discusses 129 separate pricing and capacity building initiatives, matching them against companies’ oncology portfolios. The study also examines whether companies are linking their initiatives to products on the WHO’s Essential Medicines List.

The cost of reaching the global health targets

An analysis published in *The Lancet Global Health* estimates the benefits and costs of reaching the 16 health targets of Sustainable Development Goal (SDG). The analysis includes 67 low- and middle-income countries that account for 75% of the world’s population. Achieving the SDG health targets could prevent 97 million premature deaths globally, and would require new annual investments increasing over time from US$ 134 billion currently to $371 billion by 2030. Approximately 25% of this cost is for medicines and other health products used to prevent or treat specific diseases, as well as training, outreach activities and campaigns. Modelling suggests that most of the costs can be met with domestic resources, although 32 countries will continue to need external assistance. High-income countries were not included in the analysis but other estimates show that all of them can afford to provide universal health coverage with essential health services to their citizens.

The analysis is intended as a tool to inform further research. It also highlights that achieving universal health coverage and the other health targets requires not only funding but political will and respect for human rights.

► *WHO News release, 17 July 2017.*


Framework for access to health products

*Geneva* – The WHO Essential Medicines and Health Products Programme has published a long-term framework for 2016–2030. The 2030 sustainable development agenda and the increasing globalization of health products development and supply have generated a need – and an opportunity – for WHO to adjust and strengthen its work in this area at the Organization’s headquarters, regional and country offices.

The framework provides a broad vision and strategic direction to reinforce WHO’s ability to help Member States achieve universal access to safe and quality-assured health products and universal health coverage. WHO will pursue this aim by (i) supporting needs-based innovation and reinforcing health product selection, use, procurement and supply systems, and (ii) strengthening regulatory capacity and practices. To maximize results the focus will be on specific areas such as antimicrobial resistance, controlled substances, research and development preparedness for epidemics, and appropriate regulatory pathways for emerging health products.


Fair Pricing Forum Report

*Geneva* – WHO has published the report of the Fair Pricing Forum held on 11 May 2017 in Amsterdam. The multi-stakeholder discussion was seen as a first step towards identifying an actionable agenda towards fair pricing of medicines.

The report states that fair pricing does not necessarily mean low pricing, but rather a medicines price that allows for a reasonable return on investment in exchange
for an affordable product. Governments should be enabled to play a stronger role in negotiating prices and where appropriate, incentivizing research and development with priority given to products that respond to public health needs. The need for greater transparency on costs of development and production and pricing of medicines was recognized as a recurring theme.


Draft pharmaceutical policy of India
India – The Department of Pharmaceuticals of the Government of India has circulated its Draft Pharmaceutical Policy – 2017. The policy aims to make essential drugs widely accessible at affordable prices, provide a longer term stable policy environment for the pharmaceutical sector, make India self-reliant in end-to-end indigenous drug manufacturing, ensure that medicines for domestic consumption and exports are of world class quality, and create an environment for R&D to produce innovator drugs.


WHO to develop an essential diagnostics list
Geneva – At its 2017 meeting the Expert Committee on the Selection of Essential Medicines recommended that WHO should develop an Essential Diagnostics List (EDL). Like the established Essential Medicines List (EML), the EDL is intended to provide evidence-based guidance to countries to create their own national lists of essential diagnostic tests and tools. This is expected to facilitate access to priority diagnostic tests at affordable prices.

Diagnostic tests are essential to guide the appropriate use of medicines and to monitor their effectiveness and/or toxicity. With technological advances, medicines and diagnostics are increasingly interconnected. The Committee recommended that the EDL should initially focus on in vitro diagnostics and on priority areas such as tuberculosis, malaria, HIV and hepatitis B and C, and that it should be expanded as soon as possible to include tests that can guide the use of antimicrobials and medicines for non-communicable diseases. WHO has meanwhile begun to lay the groundwork for the preparation of the list.


Preparedness

Pandemic emergency financing
Sendai, Japan – The World Bank has launched a specialized type of bonds aimed at providing financial support to the Pandemic Emergency Financing Facility (PEF), a facility that will channel funding to developing countries facing the risk of a pandemic. This marks the first time that pandemic risk in low-income countries is being transferred to the financial markets.

The PEF will provide over US$ 500 million to cover developing countries against the risk of pandemic outbreaks over the next five years. The Facility has an “insurance” window and a “cash” window that will be available from 2018 for the containment of diseases that may not be eligible for funding under the insurance window.

The creation of the PEF in May 2016 was announced at the G7 Finance Ministers and Central Governors meeting in Japan. The Facility covers six viruses that are most likely to cause a pandemic, including
new orthomyxoviruses (new influenza pandemic virus A), Coronaviridae (SARS, MERS), Filoviridae (Ebola, Marburg), and other zoonotic diseases (Crimean Congo, Rift Valley, Lassa fever). Countries eligible for financing under the PEF’s insurance window are members of the International Development Association (IDA). PEF financing will be triggered when an outbreak reaches predetermined levels of mortality and spread. The determinations for the trigger are made based on publicly available data as reported by WHO.


### Drug resistance

#### Gonorrhoea:

**WHO calls for action**

Rio de Janeiro, Brazil – At the STI & HIV World Congress, held on 9–12 July 2017, WHO has called for international collaborative action to tackle antimicrobial resistance of *Neisseria gonorrhoeae*. WHO surveillance data show that this resistance is widespread and on the rise. The findings led to an update of WHO treatment recommendations in gonorrhoea in 2016.

*N. gonorrhoeae* is listed among the WHO “High Priority” pathogens for development of new antibiotics, and is on similar priority lists in the U.S., UK and Canada. Only three new candidate medicines are at various stages of clinical development: solithromycin, zoliflodacin, and gepotidacin. Supporting the development of new antibiotic treatments for gonorrhoea is one of the key priorities of the Global Antibiotic Research and Development Partnership (GARDP), a not-for-profit organization launched in May 2016 by the Drugs for Neglected Diseases initiative (DNDi) and WHO.

In addition, non-drug measures are essential to control gonorrhoea, including information and education to promote safer sexual behaviour and encourage people to seek care, earlier diagnosis with point-of-care tests – ideally ones that can detect resistance – and effective tracking and reporting of new infections, antibiotic use, resistance and treatment failures.


#### Antimicrobials:

**EU Action plan against resistance**

Brussels – The European Commission has adopted its new One Health Action Plan to tackle antimicrobial resistance (AMR) in both humans and animals. The first deliverable of the plan will be an EU guideline on the prudent use of antimicrobials in human health. In addition, the plan foresees more than 75 actions built on three main pillars: Making the EU a best-practice region; boosting research, development and innovation; and shaping the global agenda.

AMR is responsible for 25 000 deaths and a loss of €1.5 billion in the EU every year. The new action plan builds on the first EU AMR Action Plan which ran from 2011 to 2016. Industry has expressed support for the EU leadership in the sustainable collaborative fight against antimicrobial resistance.


#### New data on antibiotics from Europe

A new report from the European Food Safety Authority (EFSA), EMA and the European Centre for Disease Prevention
and Control (ECDC) presents new data confirming the link between antibiotic consumption and antibiotic resistance in both humans and food-producing animals, and reflects improved surveillance across Europe. The findings confirm the conclusions of the first report, published in 2015, based on a more sophisticated analysis of new, better quality data.


**Antiretrovirals:**

**WHO drug resistance report**

Geneva – WHO has released its HIV drug resistance report 2017, which was co-authored by the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the U.S. Centers for Disease Control and Prevention. The report reveals an increasing trend of HIV resistance to antiretrovirals.

In 6 of 11 countries surveyed in Africa, Asia and Latin America, over 10% of people starting antiretroviral therapy had a strain of HIV that was resistant to some of the most widely used medicines – a threshold that should trigger an urgent review of national treatment guidelines according to the report findings. Mathematical modelling shows that if no action is taken, an additional 135 000 deaths and 105 000 new infections could occur and HIV treatment costs could increase by US$ 650 million in the next five years.

Of 36.7 million people living with HIV worldwide, 19.5 million people were accessing ARV therapy in 2016. In most patients the treatment remains highly effective, but a growing number are experiencing the consequences of drug resistance. WHO is issuing new guidelines to help countries address HIV drug resistance.


**Medicines use**

**Proton pump inhibitors:**

**Study warns against overuse**

A new study examines the association between the use of proton pump inhibitors (PPIs) and risk of all-cause mortality. The authors note that these products are widely prescribed, rarely deprescribed, and are available over the counter in several countries.

The risks of PPIs are well documented and include some serious adverse effects. The results of the study show an excess risk of death among PPI users, including those without gastrointestinal conditions, which increases with prolonged duration of use. The benefits of PPIs outweigh the risks if they are used for the approved indications. However, in the U.S. their use doubled between 1999 and 2012, and it has been estimated that 53-69% of PPI prescriptions are for inappropriate indications. The study concludes that may be warranted to limit PPI use and duration to instances where it is medically indicated.


**Public health**

**Hepatitis:**

**High mortality despite progress**

Geneva – On World Hepatitis Day 2017 WHO has published new data from 28 high-burden countries, showing that national
efforts for effective prevention, diagnosis, treatment and care are gaining momentum. However, hepatitis C treatment remains expensive, and there is an urgent need to scale up access to hepatitis testing.

Viral hepatitis affected 325 million people and caused 1.34 million deaths worldwide in 2015, almost as many as tuberculosis and more than HIV. Most hepatitis deaths are due to hepatitis B and C.

Hepatitis C can be cured with direct-acting antivirals (DAAs). However, in 2015 only 7% of 71 million patients had access to DAAs despite dramatic price drops in some countries. The recent WHO-prequalification of a sofosbuvir active ingredient and a generic product will promote generic competition; other hepatitis C medicines are under assessment by WHO.

Hepatitis B affects 257 million people globally. Many countries have scaled up hepatitis B vaccination, and treatment with tenofovir (which in most cases needs to be taken for life), is generally affordable; however there is an urgent need to scale up diagnostic testing.

Poliovirus

Geneva – At its fourteenth meeting held on 3 August 2017 by teleconference 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 (PHEIC) and has recommended to maintain the revised Temporary Recommendations for another 3 months. The Committee was encouraged by the steady progress achieved in all three countries infected with wild poliovirus – Pakistan, Afghanistan, and Nigeria – and the fall in the number of cases globally, with no international spread detected in the last three months. However, risks remain as polioviruses are likely to be still circulating in areas with inaccessible populations, lack of services and/or security risks. The Committee was very concerned about new outbreaks of vaccine-derived poliovirus in the Democratic Republic of the Congo and in Syria, and by the delay in detecting these outbreaks, indicating serious persisting gaps in immunization and surveillance.

The Committee strongly urged global partners to support countries in implementing the Temporary Recommendations for immunization and cross-border control at this critical time and warned against complacency, which could easily lead to a resurgence of polio.

WHO Statement, 3 August 2017.

2016 immunization coverage

Geneva – The latest joint WHO and UNICEF immunization estimates show that global immunization coverage has stalled at 86% since 2010, falling short of the target of 90%. Nearly 1 in 10 infants did not receive any vaccinations in 2016.

Worldwide, 10 million infants need to complete the full 3-dose immunization against diphtheria, tetanus and pertussis (DTP). Of these, 4 million live in just three countries – Afghanistan, Nigeria and Pakistan – where access to routine immunization services is also critical to achieving and sustaining polio eradication. 85% of children under one year globally have received a first dose of measles vaccine, 64% have received a second dose. Global coverage of rubella vaccines and the more recently recommended rotavirus and pneumonia vaccines is below 50%.
National coverage estimates often mask large inequities within countries. The report shows that there is generally less inequality now than 10 years ago, but that more efforts are needed to bring vaccines to households with low income and education levels.


**Maternal immunization safety monitoring**

Global efforts are underway to develop and implement new vaccines for use in pregnant women in low- and middle-income countries (LMICs), where there is the greatest burden of vaccine-preventable disease. As these efforts go forward, it is a critical time to formulate an organized and comprehensive approach to monitoring safety of maternal immunizations in LMICs. A new report by the Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) looks at existing programmes, identifies gaps and outlines a roadmap for effective safety monitoring of maternal immunization.

The report was developed with support from the Bill & Melinda Gates Foundation and with input from a large multidisciplinary group of experts. Reference is made to relevant work done by other organizations, such as the 2017 CIOMS Guide to Active Vaccine Safety Surveillance.


**WHO medicines prequalification updates**

**Prequalified “Firsts”**

**Medicines:**
- First etravirine API, for manufacture of HIV medicines
- First kanamycin injection, for second-line treatment of tuberculosis
- First sofosbuvir API, for manufacture of hepatitis C medicines
- First generic oxytocin, to treat bleeding after childbirth
- First generic magnesium injection, for treatment of complications in pregnancy
- First prequalified pyrimethamine, for treatment of malaria
- First generic streptomycin, for treatment of tuberculosis
- First paediatric isoniazid/rifampicin 50/75 dispersible tablet

► WHO-PQTm website. Prequalified lists:
  - Active Pharmaceutical Ingredients
  - Medicines/Finished Pharmaceutical Products

**Diagnostics:**
- First HIV self-test

► WHO list of prequalified in vitro diagnostic products

**New proposed KPIs**

WHO-PQT has proposed new key performance indicators (KPIs) to measure programme responsiveness and prequalification timelines. The document proposes a harmonized approach to calculation of timelines (both WHO time and applicants’ “stop-clock” time) as well as targets for the proposed KPIs. Once the public comment phase is concluded, the KPIs will be implemented through a new IT system that is planned to go live in October 2018.

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

Ganciclovir

(Ganciclovirum)

This is a draft proposal of a monograph for The International Pharmacopoeia (Working document QAS/16.652/Rev.1, July 2017). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

Molecular formula. $C_9H_{13}N_5O_4$

Relative molecular mass. 255.23

Graphic formula

Chemical name. 2-Amino-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one. CAS Reg. No. 82410-32-0.

Description. White or almost white, crystalline powder.

Solubility. Slightly soluble in water or glacial acetic acid, very slightly soluble in dehydrated ethanol, practically insoluble in methanol and dichloromethane. It dissolves in dilute solutions of mineral acids and alkali hydroxides.

Category. Antiviral (Purine nucleoside analogue).

Storage. Preserve in well-closed containers. Protect from light and moisture.
Additional information. Ganciclovir is hygroscopic and may exhibit polymorphism. Caution: Ganciclovir is a potent cytotoxic agent and suspected carcinogen. It must be handled with care, avoiding contact with the skin and inhalation of airborne particles.

Requirements

Definition. Ganciclovir contains not less than 99.0% and not more than 101.0% of C₉H₁₃N₅O₄, calculated with reference to the anhydrous substance.

Identity tests

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

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

If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and ganciclovir RS in a small amount of hot water R (80°C), allowing to cool in an ice-bath, filtering and drying the precipitate at 105°C for 3 hours. The infrared absorption spectrum is concordant with the spectrum obtained from ganciclovir RS.

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

B.1 Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 4 volumes of ammonia (260 g/L) TS, 40 volumes of methanol R and 60 volumes of dichloromethane R as the mobile phase. Apply separately to the plate 5 μL of each of the following three solutions. For solution (A) dissolve 10 mg of the substance to be examined in 2 mL of sodium hydroxide (~0.8 g/L) TS and dilute to 10 mL with methanol R. For solution (B) dissolve 10 mg of ganciclovir RS in 2 mL of sodium hydroxide (~0.8 g/L) TS and dilute to 10 mL with methanol R. For solution (C) dissolve 10 mg of ganciclovir RS and 10 mg of aciclovir R in 2 mL of sodium hydroxide (~0.8 g/L) TS and dilute to 10 mL with methanol R. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air and examine the chromatogram under ultraviolet light (254 nm). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots. The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to ganciclovir in the chromatogram obtained with solution (B).

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described above under test B.1 but using silica gel R5 as the coating substance. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air or heat the plate for five minutes at 120°C. Spray the plate with Dragendorff reagent TS and allow it to dry exhaustively in air. Then spray the plate with a mixture of sulfuric acid (~1760 g/L) TS and dehydrated ethanol R (1:1). Examine the chromatogram in daylight. The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots. The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and
intensity with the spot due to ganciclovir in the chromatogram obtained with solution (B).

C. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Related substances”. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the ganciclovir peak in the chromatogram obtained with solution (3).

D. Dissolve about 5 mg of the sample in 500 mL of water R. The absorption spectrum (1.6) of this solution, when observed between 200 nm and 300 nm, exhibits a minimum at about 222 nm and a maximum at about 252 nm with a shoulder at about 275 nm.

Clarity and colour of solution. Dissolve 1.25 g in sodium hydroxide (~40 g/L) TS and dilute to 25 mL. This solution is clear and not more intensely coloured than reference solution Y5, when compared as described under 1.11.2 Degree of coloration of liquids, Method II.

[Note from the Secretariat. The chapter 1.11 Colour of liquids is currently under revision. Reference is already made to a new test procedure to be added under the section 1.11.2 Degree of coloration of liquids in the 7th Edition of The International Pharmacopoeia.]

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 content of heavy metals according to Method A; not more than 10 μg/g.

Sulfated ash (2.3). Not more than 1.0 mg/g.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using 0.300 g of the substance and methanol as solvent. The substance to be examined has a limited solubility in methanol and will appear as a slurry. Replace the solvent after each titration. The water content is not more than 40 mg/g.

Related substances. Carry out the test as described under 1.14.4 High performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded strong acidic cation-exchange groups (3–10 μm).¹

Use the following mobile phase: Dilute 0.5 mL of trifluoroacetic acid R to 1000 mL with water R. Mix 500 volumes of this solution with 500 volumes of acetonitrile R.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm. Maintain the column at 40°C.

Prepare the following solutions using mobile phase as a diluent. For solution (1) dissolve about 30 mg of the test substance using sonication and dilute to 50.0 mL. For solution (2) dilute 1 volume of solution (1) to 1000 volumes. For solution (3) dissolve 3.0 mg of ganciclovir RS using sonication and dilute to 5.0 mL. For solution (4) dissolve the content of a vial of ganciclovir for system suitability RS (containing the impurities A, B, C, D, E and F) in 1.0 mL of solution (3).

Inject alternately 20 μL each of solutions (1), (2), (3) and (4). Record the chromatograms for about 2.5 times the retention time of ganciclovir (retention time about 14 minutes).

¹ A Thermo BioBasic SCX column (4.6 mm × 250 mm, 5 μm) has been found suitable.
Ganciclovir (Ph. Int.)

Use the chromatogram supplied with ganciclovir for system suitability RS and the chromatograms obtained with reference solution (3) and (4) to identify the peaks due to ganciclovir and the impurities A, B, C, D, E and F. The following peaks are eluted at the following relative retention with reference to the peak of ganciclovir: impurity A about 0.6; impurity B about 0.67; impurity C about 0.71; impurity D about 0.8; impurity E about 0.9; impurity F about 2.0.

The test is not valid unless in the chromatogram obtained with solution (4) the peak-to-valley ratio \((H_p/H_v)\) is at least 5, where \(H_p\) is the height above the baseline of the peak due to impurity E and \(H_v\) is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ganciclovir.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, C, D or E is not greater than 1.5 times the area of the peak due to ganciclovir in the chromatogram obtained with solution (2) (0.15%);
- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.3, is not greater than twice the area of the peak due to ganciclovir in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to impurity F, when multiplied by a correction factor of 0.7, is not greater than 4 times the area of the peak due to ganciclovir in the chromatogram obtained with solution (2) (0.4%);
- the area of any other impurity peak is not greater than 0.5 times the area of the peak due to ganciclovir in the chromatogram obtained with solution (2) (0.05%);
- the sum of the corrected areas of the peaks corresponding to impurity B and impurity F and the areas of all other impurity peaks is not greater than 6 times the area of the peak due to ganciclovir in the chromatogram obtained with solution (2) (0.6%). Disregard any peak with an area less than 0.3 times the area of the peak due to ganciclovir obtained with solution (2) (0.03%).

**Assay.** Dissolve about 0.200 g, accurately weighed, in 10 mL of anhydrous formic acid R and dilute to 60 mL with anhydrous glacial acetic acid R. Titrate with perchloric acid (0.1 mol/L) VS, determining the end-point potentiometrically as described under 2.6 Non-aqueous titration. Carry out a blank titration. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 25.52 mg of ganciclovir \((C_9H_{13}N_5O_4)\).

**Additional requirements for Ganciclovir for parenteral use**

Complies with the monograph for Parenteral preparations.

**Bacterial endotoxins.** If intended for use in the manufacture of a parenteral dosage form without a further appropriate procedure for the removal of bacterial endotoxins, carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 0.84 IU of endotoxin RS per mg of ganciclovir.
Impurities

[Note from the Secretariat. The impurities will be brought into alphabetical order at a later stage of the monograph development.]

A. $R = \text{CH}_2\text{-O-CH}_2\text{-CCl-CH}_2$: 2-amino-9-[[2-chloroprop-2-en-1-yl]oxy]methyl]-1,9-dihydro-6H-purin-6-one (synthesis-related impurity),

D. $R = \text{CH}_2\text{-O-CH}_2\text{-O-CH(CH}_2\text{OH)}$: 2-amino-9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one (synthesis-related impurity),

F. $R = \text{H}$: 2-amino-1,9-dihydro-6H-purin-6-one (guanine) (synthesis-related impurity, degradation product),

B. $R = \text{O-CO-CH}_2\text{-CH}_3$: (2RS)-2-[(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]-3-hydroxypropyl propionate (synthesis-related impurity),

C. $R = \text{Cl}$: 2-amino-9-[[1RS]-2-chloro-1-(hydroxymethyl)ethoxy]methyl]-1,9-dihydro-6H-purin-6-one (synthesis-related impurity),

E. 2-amino-9-[[2RS]-2,3-dihydroxypropoxy]methyl]-1,9-dihydro-6H-purin-6-one (synthesis-related impurity),

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H. 2-amino-7-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]-1,7-dihydro-6H-purin-6-one (synthesis-related impurity),

I. \( R = H \): 2-[(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]propane-1,3-diyl dipropanoate (synthesis-related impurity),

J. \( R = \text{CO-CH}_2\text{-CH}_3 \): 2-[2-(propanoylamino)-6-oxo-1,6-dihydro-9H-purin-9-yl] methoxy]propane-1,3-diyl dipropanoate (synthesis-related impurity).

**New reference substances**

Ganciclovir RS

Ganciclovir for system suitability RS (containing the impurities A, B, C, D, E and F)

**New reagent**

Aciclovir R

Aciclovir of a suitable quality should be used.

***
**Ganciclovir for injection**  
*(Gancicloviri ad injectionem)*

This is a draft proposal of a monograph for *The International Pharmacopoeia*  

**Description.** A white powder or loose lumps.

**Category.** Antiviral (Purine nucleoside analogue).

**Storage.** Ganciclovir for injection should be kept in a tightly closed container, protected from moisture and light.

**Additional information.** Ganciclovir for injection 500 mg is listed on the 12th invitation to manufacturers of medicinal products for HIV infection and related diseases to submit an Expression of Interest (EOI) for product evaluation to the WHO Prequalification of Medicines Team. Handle Ganciclovir for injection with great care because it is a potent cytotoxic agent and suspected carcinogen.

Ganciclovir for injection is hygroscopic.

**Requirements**

The powder for injection and the reconstituted solution for injection complies with the monograph for *Parenteral preparations*.

**Definition.** Ganciclovir for injection is a freeze-dried powder prepared by the neutralization of Ganciclovir with the aid of sodium hydroxide. Ganciclovir for injection contains not less than 90.0% and not more than 110.0% of the labelled amount of ganciclovir (C₉H₁₃N₅O₄).

**Identity tests**

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

A. Dilute a quantity of the test substance, containing the equivalent of about 0.2 g of Ganciclovir with 10 mL water R. Adjust the suspension to pH 6–7 with hydrochloric acid (0.1 mol/L) TS and allow to stand for 30 minutes. Filter the suspension, wash the filtrate with 20 mL water R and dry it at 105°C for 3 hours. Carry out the test as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the reference spectrum of ganciclovir or with the spectrum obtained from ganciclovir RS treated similarly.

If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the dried filtrate and ganciclovir RS in a small amount of hot water R (80°C), allowing to cool in an ice-bath, filtering and drying the precipitate at 105°C for 3 hours. The infrared absorption spectrum is concordant with the spectrum obtained from ganciclovir RS.
Ganciclovir for injection (Ph. Int.)

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

B.1 Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 4 volumes of ammonia (260 g/L) TS, 40 volumes of methanol R and 60 volumes of dichloromethane R as the mobile phase. Apply separately to the plate 5 μL of each of the following three solutions. For solution (A) dissolve a quantity of the test substance, containing the equivalent of about 10 mg of ganciclovir in 2 mL water R and dilute to 10 mL with methanol R. For solution (B) dissolve 10 mg of ganciclovir RS in 2 mL of sodium hydroxide (0.8 g/L) TS and dilute to 10 mL with methanol R. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air and examine the chromatogram under ultraviolet light (254 nm). The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to ganciclovir in the chromatogram obtained with solution (B).

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described above under test B.1 but using silica gel R5 as the coating substance. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air or heat the plate for five minutes at 120°C. Spray the plate with Dragendorff reagent TS and allow it to dry exhaustively in air. Then spray the plate with a mixture of sulfuric acid (~1760 g/L) TS and dehydrated ethanol R (1:1). Examine the chromatogram in daylight. The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots. The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to ganciclovir in the chromatogram obtained with solution (B).

C. 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 ganciclovir in the chromatogram obtained with solution (2).

D. Dissolve a quantity of the powder for injection equivalent to 20 mg of ganciclovir in 2 mL hydrochloric acid (~420 g/L) TS, evaporate the solution to dryness on a hot water-bath, add 1 mL hydrochloric acid (~420 g/L) TS and about 30 mg potassium chlorate R. Then evaporate the solution to dryness on a hot water-bath and add drops of ammonia (~100 g/L) TS to the residues; a violet-red colour is produced. Add drops of sodium hydroxide (~40 g/L) TS and the violet-red colour disappears.

pH value (1.13). pH of a solution containing the equivalent to 12.5 mg of ganciclovir per mL of water R, 10.5–11.5.

Clarity and colour of solution. A solution, containing the equivalent to 0.10 g of ganciclovir in 10 mL of water R, is clear and not more intensely coloured than reference solution Y5, when compared as described under 1.11.2 Degree of coloration of liquids, Method II.

[Note from the Secretariat. The chapter 1.11 Colour of liquids is currently under revision. Reference is already made to a new test procedure to be added under the section 1.11.2 Degree of coloration of liquids.]
**Water.** Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using 0.300 g of the substance and methanol as solvent. The substance to be examined has a limited solubility in methanol and will appear as a slurry. Replace the solvent after each titration. The water content is not more than 30 mg/g.

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

Prepare the following solutions using mobile phase as a diluent. For test solution (1) dissolve a quantity of the powder for injection, containing the equivalent of about 30 mg ganciclovir, using sonication, and dilute to 50.0 mL. For solution (2) dilute 1 volume of solution (1) to 1000 volumes. For solution (3) dissolve 3.0 mg of ganciclovir RS and dilute to 5.0 mL. For solution (4) dissolve the content of a vial of ganciclovir for system suitability RS (containing the impurities A, B, C, D, E and F) in 1.0 mL of solution (3).

Inject alternately 20 μL each of solutions (1), (2), (3) and (4). Record the chromatograms for 2.5 times of the retention time of ganciclovir (retention time about 14 minutes).

Use the chromatogram supplied with ganciclovir for system suitability RS and the chromatogram obtained with reference solution (4) to identify the peaks due to ganciclovir and the impurities A, B, C, D, E and F. The following peaks are eluted at the following relative retention with reference to the peak of ganciclovir: impurity A = about 0.6; impurity B = about 0.67; impurity C = about 0.71; impurity D = about 0.8; impurity E = about 0.9; impurity F = about 2.0.

The test is not valid unless in the chromatogram obtained with solution (4) the peak-to-valley ratio (Hₚ/Hᵥ) is at least 5, where Hₚ is the height above the baseline of the peak due to impurity E and Hᵥ is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ganciclovir.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity F, when multiplied by a correction factor of 0.7, is not greater than 4 times the area of the peak due to ganciclovir in the chromatogram obtained with solution (2) (0.4%);

**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 strong acidic cation-exchange groups (3–10 μm).¹

Use the following mobile phase: Dilute 0.5 mL of trifluoroacetic acid R to 1000 mL with water R. Mix 500 volumes of this solution with 500 volumes of acetonitrile R.

Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm. Maintain the column at 40°C.

Weigh and mix the contents of 5 containers. Prepare the following solutions in mobile phase. For solution (1) dissolve a quantity of the powder of injection, equivalent to about 30.0 mg of ganciclovir, accurately weighed, and dilute to 50.0 mL. Dilute 10.0 mL of this solution to

¹ The Thermo BioBasic SCX column (4.6 mm × 250 mm, 5 μm) has been found suitable.
Ganciclovir for injection (Ph. Int.)

100.0 mL. For solution (2) dissolve 15.0 mg of ganciclovir RS, and dilute to 25.0 mL. Dilute 10.0 mL of this solution to 100.0 mL.

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

Measure the areas of the peaks corresponding to ganciclovir in the chromatograms of solution (1) and (2) and calculate the percentage content of ganciclovir (C₉H₁₃N₅O₄) per container, using the declared content of C₉H₁₃N₅O₄ in ganciclovir RS.

**Bacterial endotoxins.** Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 0.84 IU of endotoxin per mg of ganciclovir.

**Impurities**
- The impurities limited by the requirements of this monograph include impurity F listed in the monograph on Ganciclovir.
Protionamide
(Protionamidum)

This is a draft proposal of a monograph for The International Pharmacopoeia (Working document QAS/17.722/Rev.2, July 2017). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

Molecular formula. \(\text{C}_9\text{H}_{12}\text{N}_2\text{S}\)

Relative molecular mass. 180.3

Graphic formula

\[
\text{N} \quad \text{CH}_2\text{CH}_2\text{CH}_3 \\
\text{CSNH}_2
\]

Chemical name. 2-Propylthioisonicotinamide; 2-propyl-4-pyridinecarbothioamide; CAS Reg. No. 14222-60-7.

Description. Yellow crystals or a crystalline powder.

Solubility. Practically insoluble in water; soluble in dehydrated ethanol R and methanol R; slightly soluble in ether R.

Category. Tuberculostatic.

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

Additional information. Protionamide may exhibit polymorphism.

Requirements

Definition. Protionamide contains not less than 99.0% and not more than 101.0% of \(\text{C}_9\text{H}_{12}\text{N}_2\text{S}\), calculated with reference to the dried substance.

Identity tests

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

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

   If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the test substance and protionamide RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from protionamide RS.
B. The absorption spectrum of a 10 μg/mL solution of the test substance in ethanol (~750 g/L) TS, when observed between 230 nm and 350 nm, exhibits a maximum at about 291 nm and a minimum at 256 nm.

C. Carry out the test as described under High-performance liquid chromatography using the conditions given under “Related substances”. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to protionamide in the chromatogram obtained with solution (3).

Heavy metals. Use 1.0 g for the preparation of the test solution as described under Limit test for heavy metals, Procedure 3. Determine the heavy metals content according to Method A; not more than 20 μg/g.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry 1.000 g of the test substance to constant weight at 105°C; it loses not more than 5.0 mg/g.

Acidity. Dissolve 2.0 g in 20 mL of methanol R by warming. Add 20 mL of water R, shake and cool to precipitate protionamide. Add 2 drops of cresol red/ethanol TS and titrate with sodium hydroxide (0.1 mol/L) VS. Not more than 0.20 mL is required to change the colour of the indicator.

Related substances. Carry out the test as described under High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel for chromatography R (5 μm).¹

As the mobile phase use a mixture of 72 volumes of a buffer solution, prepared by mixing 2.0 mL of triethylamine R with 1000 mL water and adjusting the pH to 6.0 with phosphoric acid (~105 g/L) TS, and 28 volumes of acetonitrile R.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 290 nm.

Prepare the following solutions in mobile phase. For solution (1) dissolve about 50 mg of the test substance in 100.0 mL. For solution (2) dilute 1 volume of solution (1) to 200 volumes. For solution (3) use a solution containing 0.05 mg of protionamide RS and 0.01 mg of ethionamide R per mL.

Inject 20 μL of solution (3). Ethionamide is eluted at a relative retention of about 0.6 with reference to protionamide (retention time about 10 minutes). The test is not valid unless the resolution between the peaks due to ethionamide and protionamide is at least 5.0.

Inject alternately 20 μL each of solution (1) and (2). Record the chromatograms for 2 times the retention time of protionamide.

In the chromatogram obtained with solution (1):

¹ Inertsil ODS was found suitable.
WHO Drug Information Vol. 31, No. 3, 2017 Consultation documents

- the area of any peak corresponding to impurity A (ethionamide), is not greater than the area of the peak due to protionamide in the chromatogram obtained with solution (2) (0.5%);
- the area of any impurity peak is not greater than 0.4 times the area of the peak due to protionamide 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 protionamide in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.2 times the area of the principal peak obtained with solution (2) (0.10%).

Assay. Dissolve about 0.45 g, accurately weighed, in 30 mL of glacial acetic acid R1 and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 18.03 mg of C₉H₁₂N₂S.

Impurity

A. 2-Ethylthioisonicotinamide; 2-ethyl-4-pyridinecarbothioamide (ethionamide).

Reference substance to be established

Protionamide RS

Reagent to be established

Ethionamide R

Ethionamide of a suitable quality should be used.

***
Protionamide tablets

(*Protionamidi compressi*)

This is a draft proposal of a monograph for *The International Pharmacopoeia* (Working document QAS/17.723/Rev.2, July 2017). The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality_safety/quality_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).

**Category.** Tuberculostatic.

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

**Additional information.** Strength in the current WHO Model List of Essential Medicines (EML): 125 mg; 250 mg. Strength in the current WHO EML for children: 125 mg; 250 mg.

**Requirements**

Comply with the monograph for Tablets.

**Definition.** Protionamide tablets contain not less than 90.0% and not more than 110.0% of the amount of protionamide (C₉H₁₂N₂S) stated on the label.

**Identity tests**

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

A. Extract a quantity of the powered tablets containing about 25 mg of protionamide with 5 mL of methanol R, filtrate and evaporate the filtrate to dryness. 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 protionamide RS or with the reference spectrum of protionamide.

If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the test substance and protionamide RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from protionamide RS.

B. To a quantity of powdered tablets containing the equivalent of about 2.5 mg of protionamide add 25 mL ethanol (~750 g/L) TS, shake and filter. Dilute 1 mL of the filtrate to 10 mL with the same solvent. The absorption spectrum (1.6) of the resulting solution, when observed between 230 nm and 350 nm, exhibits a maximum at about 291 nm and a minimum at 256 nm.

C. 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 principle peak in the chromatogram obtained from solution (1) corresponds to the retention time of the peak due to protionamide 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 (~4 g/L) TS and rotating the paddle at 100 revolutions per minute. At 30 minutes withdraw a sample of 10 mL of the medium through an in-line filter and 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 if necessary, at a wavelength of 277 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 protionamide RS in the dissolution medium.

For each of the tablets tested, calculate the total amount of protionamide (C₉H₁₂N₂S) in the dissolution medium from the absorbances obtained. Evaluate the results as described under 5.5 Dissolution test for solid dosage forms. The amount of protionamide in solution for each tablet is not less than 75% (Q) of the amount stated on the label.

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

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

For solution (1) transfer a quantity of the powdered tablets equivalent to about 250 mg of protionamide, accurately weighed, into a 250 mL volumetric flask, disperse in 100 mL, shake vigorously and dilute to volume. Filter the resulting solution and dilute 25.0 mL of this solution to 50.0 mL. For solution (2) dilute 1 volume of solution (1) to 100 volumes with mobile phase. For solution (3) use a solution containing 0.05 mg of protionamide RS and 0.01 mg of ethionamide R per mL mobile phase.

Inject 20 µL of solution (3). Ethionamide is eluted at a relative retention of about 0.6 with reference to protionamide (retention time about 10 minutes). The test is not valid unless the resolution between the peaks due to ethionamide and protionamide is at least 5.0.

Inject alternately 20 µL each of solution (1) and (2). Record the chromatograms for 2 times the retention time of protionamide.

In the chromatogram obtained with solution (1):

- the area of any impurity peak is not greater than the area of the peak due to protionamide in the chromatogram obtained with solution (2) (0.5%).

**Assay.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm ×4.6 mm) packed with particles of silica gel for chromatography R (5 μm).¹

As the mobile phase use a mixture of 72 volumes of a buffer solution prepared by mixing 2.0 mL of triethylamine R with 1000 mL water and adjusting the pH to 6.0 with phosphoric acid (~105 g/L) TS and 28 volumes of acetonitrile R.

Operate with a flow rate of 1 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 290 nm.

¹ Inertsil ODS was found suitable.
Prepare the following solutions in mobile phase. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing about 250 mg of protionamide, accurately weighed, into a 250 mL volumetric flask, disperse in 100 mL, shake vigorously and dilute to volume. Filter the resulting solution and dilute 10.0 mL of this solution to 200.0 mL. For solution (2) dilute 50.0 mg of protionamide RS and 10.0 mg of ethionamide R in 100.0 mL. Dilute 10.0 mL of this solution to 100.0 mL.

Inject 20 μL of solution (2). Ethionamide is eluted at a relative retention of about 0.6 with reference to protionamide (retention time about 10 minutes). The test is not valid unless the resolution between the peaks due to ethionamide and protionamide is at least 5.0.

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

Measure the areas of the peaks corresponding to protionamide obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of protionamide (C₉H₁₂N₂S) in the tablets, using the declared content of protionamide (C₉H₁₂N₂S) in protionamide RS.

Impurities

The impurities limited by the requirements of this monograph include the impurity listed in the monograph on Protionamide.

Reference substance to be established

Protionamide RS
Reagent to be established

Ethionamide R
Ethionamide of a suitable quality should be used.
Norethisterone enantate
(Norethisteroni enantas)

This is a draft proposal of a monograph for The International Pharmacopoeia (Working document QAS/17.724/Rev.2, July 2017). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

Molecular formula. $C_{27}H_{38}O_3$

Relative molecular mass. 410.6

Chemical names. 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one heptanoate; 17-[(1-oxoheptyl)oxy]-19-nor-17α-pregn-4-en-20-yn-3-one; CAS Reg. No. 3836-23-5.

Other name. Norethindrone enantate.

Description. A white to yellowish white, crystalline powder.

Solubility. Practically insoluble in water R; freely soluble in acetone R, methanol R, dehydrated ethanol R and dioxan R.

Category. Contraceptive.

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

Requirements

Norethisterone enantate contains not less than 98.0% and not more than 102.0% (“Assay”, Method A) or not less than 97.0% and not more than 102.0% (“Assay”, Method B) of $C_{27}H_{38}O_3$, calculated with reference to the dried substance.

Identity tests

- Either test A alone or tests B and C may be applied.
- A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from norethisterone enantate RS or with the reference spectrum of norethisterone enantate.
Norethisterone enantate (Ph. Int.)

The absorption spectrum (1) of a solution of about 15 μg of the test substance per mL in methanol R, when observed between 210 nm and 290 nm, exhibits a maximum at about 240 nm.

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

Specific optical rotation. Use a 20 mg/mL solution in dichloromethan R; \( [\alpha]_D^{20^\circ} = -10.0^\circ \) to \(-15.0^\circ \).

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry over desiccant silica gel R at ambient temperature for 4 hours; it loses not more than 5.0 mg/g.

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

Prepare the following solutions in methanol R. For solution (1) dilute a suitable amount of sample to obtain a concentration of 1.0 mg of Norethisterone enantate per mL. For solution (2) dilute 1 volume of solution (1) to 100 volumes. For solution (3) prepare a solution containing 1.0 mg per mL of norethisterone enantate RS and 0.1 mg per mL of norethisterone caproate R.

Inject 20 μL of solution (3). The test is not valid unless the resolution between the peak due to norethisterone caproate (with a relative retention of about 0.95) and the peak due to norethisterone enantate (retention time about 27 minutes) is at least 4.0.

Inject alternatively 20 μL of solutions (1) and (2).

In the chromatogram obtained with solution (1):

- the area of any impurity peak is not greater than 0.3 times the area of the peak due to norethisterone enantate in the chromatogram obtained with solution (2) (0.3%);
- the sum of the areas of all impurities is not greater than the area of the peak due to norethisterone enantate in the chromatogram obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.05 times the area of the peak due to norethisterone enantate in the chromatogram obtained with solution (2) (0.05%).

Free enantionic acid. Dissolve 0.3 g in 10 mL of neutralized ethanol (~750 g/L) TS. Titrate the solution quickly with sodium hydroxide (0.01 mol/L) VS to a light blue end-point using bromothymol blue/ethanol TS as indicator; not more than 0.3 mL (corresponding to 1.3 mg/g of enantionic acid).

Assay

- Either method A or B may be applied.

A. Dissolve about 15 mg, accurately weighed, in sufficient methanol R and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of this solution to 100.0 mL with methanol R.
Measure the absorbance of the diluted solution in a 1 cm layer at the maximum at about 240 nm and calculate the content of C\textsubscript{27}H\textsubscript{38}O\textsubscript{3} using the absorptivity value of 42.8 (A\textsubscript{1cm} = 428).

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

Use the following conditions for gradient elution:

- mobile phase A: water R;
- mobile phase B: acetonitrile R.

<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>0–17</td>
<td>40</td>
<td>60</td>
<td>Isocratic</td>
</tr>
<tr>
<td>17–20</td>
<td>40 to 10</td>
<td>60 to 90</td>
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<td>10</td>
<td>90</td>
<td>Isocratic</td>
</tr>
<tr>
<td>45–46</td>
<td>10 to 40</td>
<td>90 to 60</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>46–60</td>
<td>40</td>
<td>60</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

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. Maintain the column temperature at 40°C.

Prepare the following solutions in methanol R. For solution (1) dissolve 20.0 mg of the test substance and dilute to 100.0 mL. For solution (2) dissolve 20.0 mg of norethisterone enantate RS and dilute to 100.0 mL.

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

Measure the areas of the peaks corresponding to norethisterone enantate obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of C\textsubscript{27}H\textsubscript{38}O\textsubscript{3} using the declared content of C\textsubscript{27}H\textsubscript{38}O\textsubscript{3} in norethisterone enantate RS.

**Additional requirement for Norethisterone enantate for parenteral use**

Complies with the monograph for Parenteral preparations.

**Reagent to be established**

**Norethisterone caproate R**

Norethisterone caproate of a suitable quality should be used.

---

1 BDS HYPERSIL C\textsubscript{18} is suitable.
Norethisterone enantate injection
(Norethisteroni enantas injectio)

This is a draft proposal of a monograph for The International Pharmacopoeia (Working document QAS/17.725/Rev.2, July 2017). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

Description. A clear, colourless or almost colourless, oily solution.

Category. Contraceptive.

Storage. Norethisterone enantate injection should be kept in a tightly closed container, protected from light.

Labelling. The oil used in the formulation should be indicated.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML): 200 mg/mL in 1 mL ampoule.

Requirements

Complies with the monograph for Parenteral preparations.

Definition. Norethisterone enantate injection contains not less than 90.0% and not more than 110.0% of the amount of Norethisterone enantate \( \text{C}_{27}\text{H}_{38}\text{O}_3 \) stated on the label.

Identity tests

- Either test A or test B may be applied.

A. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions as 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 norethisterone enantate in the chromatogram obtained with solution (2).

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 2 volumes of cyclohexane R and 1 volume of ethyl acetate R as the mobile phase. Apply separately to the plate 10 µL of each of the following two solutions in dichloromethane R. For solution (A) use a dilution of the test solution containing the equivalent of 1.0 mg of Norethisterone enantate per mL. For solution (B) use a solution containing 1.0 mg of norethisterone enantate RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm). Spray the plate with antimony trichloride TS, heat at 110°C for 15 minutes and examine the chromatogram in ultraviolet light (365 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).
Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 1.5 IU of endotoxin RS per mg.

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

Prepare the following solutions in methanol R. For solution (1) dilute a suitable volume of the sample to obtain a concentration of 1.0 mg of Norethisterone enantate per mL. For solution (2) dilute 1 volume of solution (1) to 100 volumes. For solution (3) use a solution containing 0.1 mg of benzyl benzoate R per mL. For solution (4) use a solution containing 1.0 mg per mL of norethisterone enantate RS and 0.1 mg per mL of norethisterone caproate R.

Inject 20 μL of solution (4). The test is not valid unless the resolution between the peak due to norethisterone caproate (with a relative retention of about 0.95) and the peak due to norethisterone enantate (retention time about 27 minutes) is at least 4.0.

Inject alternatively 20 μL of solutions (1), (2) and (3) and record the chromatograms. Use the chromatogram obtained with solution (3) to identify any peak due to benzyl benzoate, if present.

In the chromatogram obtained with solution (1):
• the area of any impurity peak is not greater than 0.5 times the area of the peak due to norethisterone enantate in the chromatogram obtained with solution (2) (0.5%);
• the sum of the areas of all impurities is not greater than the area of the peak due to norethisterone enantate in the chromatogram obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak obtained with solution (2) (0.1%) and disregard any peak due to benzyl benzoate.

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

Use the following conditions for gradient elution:

- mobile phase A: water;
- mobile phase B: acetonitrile R.

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<td>46–60</td>
<td>40</td>
<td>60</td>
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</tr>
</tbody>
</table>

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. Maintain the column temperature at 40°C.

¹ BDS HYPERSIL C₁₈ is suitable
Norethisterone enantate injection (Ph. Int.)

Prepare the following solution in methanol R. For solution (1) dilute 1.0 mL of the injection to 100.0 mL. Dilute 10.0 mL of this solution to 100.0 mL. For solution (2) dissolve 20.0 mg of norethisterone enantate RS and dilute to 100.0 mL.

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

Measure the areas of the peaks corresponding to norethisterone enantate obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of $C_{27}H_{38}O_3$ using the declared content of $C_{27}H_{38}O_3$ in norethisterone enantate RS.

***
This is a draft proposed revision of a monograph for *The International Pharmacopoeia* (Working document QAS/17.701, August 2017). 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 based on information found in the European Pharmacopoeia and the United States Pharmacopeia.]

Ciclosporin
*(Ciclosporinum)*

Molecular formula. $C_{62}H_{111}N_{11}O_{12}$

Relative molecular mass. 1203

Chemical name

Other name. Cyclosporin.

Description. A white or almost white powder.

Solubility. Practically insoluble in water; freely soluble in ethanol (~750 g/L) TS and dichloromethane R.

Category. Immunosuppressant.

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

Additional information. Ciclosporin is a product derived from a fermentation process or obtained by other ways.

Requirements

Definition. Ciclosporin contains not less than 97.0% and not more than 102.0% of $C_{62}H_{111}N_{11}O_{12}$, calculated with reference to the dried substance.
Identity tests

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

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

B. Carry out 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 ciclosporin in the chromatogram obtained with solution (2).

C. Dissolve 5 mg in 5 mL of methanol R, and 1 drop of potassium permanganate (10 g/L) TS and allow to stand; the blue-red colour is gradually discharged.

Specific optical rotation. Use a 5.0 mg/mL solution in methanol R and calculate with reference to the dried substance; \( \kappa^\circ_{D} = -193^\circ \) to \(-185^\circ \).

Heavy metals. Use 1.0 g of the test substance 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.

Clarity and colour of solution in ethanol. A solution of 1.5 g in 15 mL of ethanol (~750 g/L) TS is clear and not more intensely coloured than standard colour solution Y₅, BY₅ or R₇ when compared as described under 1.11.2 Colour of liquids.

(Note from the Secretariat. The chapter 1.11 Colour of liquids is currently under revision. Reference is already made to a new test procedure to be added under the section 1.11.2 Degree of coloration of liquids.)

Sulfated ash (2.3). Not more than 1.0 mg/g.

Loss on drying. Dry 1.000 g of the test substance at 60°C under reduced pressure (not exceeding 15 Pa) for 3 hours; it loses not more than 20 mg/g.

Related substances. Carry out the test as described below under “Assay”.

Prepare the following solutions in a mixture of equal volumes of acetonitrile R and water R. For solution (1) dissolve 30.0 mg of the test substance and dilute to 25.0 mL. For solution (2) dilute 2.0 mL of solution (1) to 200 mL. For solution (3) prepare a solution containing 1.0 mg of ciclosporin for system suitability RS (containing a 100:1 (w/w) mixture of ciclosporin and ciclosporin U) per mL.

Inject 20 μL of solution (3). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 1.4, where Hp is the height above the baseline of the peak due to ciclosporin U and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ciclosporin (retention time 25 to 30 minutes).

Inject alternately 20 μL each of solutions (1) and (2). Record the chromatograms for 1.7 times the retention time of the principal peak.
In the chromatogram obtained with solution (1):

- the area of any impurity peak, is not greater than 0.7 times the area of the peak due to ciclosporin in the chromatogram obtained with solution (2) (0.7%),
- the sum of the areas of all impurities is not greater than 1.5 times the area of the peak due to cyclosporine in the chromatogram obtained with solution (2) (1.5%). Disregard any peak with an area less than 0.05 times the area of the peak due to ciclosporin in the chromatogram obtained with solution (2) (0.05%).

**Assay.** Determine as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3–5 μm). The column is connected to the injection port by a steel capillary tube about 1 m long with an internal diameter of 0.25 mm. Maintain the temperature of the column and of the steel capillary at 80°C. As the mobile phase use a mixture of 52 volumes of water, 43 volumes of acetonitrile R, 5 volumes of tert-butyl methyl ether R and 0.1 volume of phosphoric acid (~1440 g/L) TS.

Prepare the following solutions in a mixture of equal volumes of acetonitrile R and water R. For solution (1) dissolve 30.0 mg of the test substance and dilute to 25.0 mL. For solution (2) dissolve 30.0 mg of cyclosporine RS and dilute to 25.0 mL. For solution (3) dilute 2.0 mL of solution (2) to 200 mL. For solution (4) prepare a solution containing 1.0 mg of ciclosporin for system suitability RS (containing a 100:1 (w/w) mixture of ciclosporin and ciclosporin U) per mL.

Operate with a flow rate of about 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 210 nm.

Inject 20 μL of solution (4). The assay is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 1.4, where Hp is the height above the baseline of the peak due to ciclosporin U and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ciclosporin (retention time 25 to 30 minutes). Inject alternately 20 μL each of solutions (1) and (2). Record the chromatograms for 1.7 times the retention time of the principal peak.

Measure the areas of the peaks corresponding to ciclosporin obtained in the chromatograms and calculate the percentage content of C_{62}H_{111}N_{11}O_{12}, using the declared content of C_{62}H_{111}N_{11}O_{12} in ciclosporin RS.
Impurities

A. different ciclosporins [difference from ciclosporin (R = CH₃; ciclosporin A)]:
ciclosporin B [7-l-Ala]; ciclosporin C [7-l-Thr]; ciclosporin D [7-l-Val]; ciclosporin E [5-l-Val];
ciclosporin G [7-(l-2-aminopentanoyl)]; ciclosporin H [5-d-MeVal]; ciclosporin L [R = H];
ciclosporin T [4-l-Leu]; ciclosporin U [11-l-Leu]; ciclosporin V [1-l-Abu]

B. [6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanoic acid]]ciclosporin A,
C. isociclosporin A.

Reference substances to be established

Ciclosporine RS
Ciclosporine for system suitability RS

***
Dacarbazine
(Dacarbazinum)

This is a draft proposed revision of a monograph for The International Pharmacopoeia (Working document QAS/17.711, August 2017). 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 Dacarbazine based on information found in the United States Pharmacopoeia, in the European Pharmacopoeia and in the scientific literature.

Molecular formula. C₆H₁₀N₆O
Relative molecular mass. 182.2

Graphic formula

Chemical name. 5-(3,3-dimethyltriaz-1-en-1-yl)-1H-imidazole-4-carboxamide; CAS Reg. No. 4342-03-4.

Description. A colourless or pale yellow, crystalline powder.

Solubility. Slightly soluble in water and ethanol (~750 g/L) TS, practically insoluble in Dichloromethane R.

Category. Cytotoxic drug.

Storage. Dacarbazine should be kept in a tightly closed container, protected from light, and stored at a temperature not exceeding 8°C.

Additional information. CAUTION: Dacarbazine must be handled with care, avoiding contact with the skin and inhalation of airborne particles.

Requirements

Dacarbazine contains not less than 98.5% and not more than 101.0% of C₆H₁₀N₆O, calculated with reference to the anhydrous substance.

Identity tests
• Either test A alone or tests B and C may be applied.
A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from dacarbazine RS or with the reference spectrum of dacarbazine.

B. The absorption spectrum of a 6 μg/mL solution in hydrochloric acid (~4 g/L) TS, when observed between 200 nm and 400 nm, exhibits a maximum at about 323 nm and a pronounced shoulder at 275 nm.

C. 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 glacial acetic acid R, water R and butanol R (1:2:5 V/V/V) as the mobile phase. Apply separately to the plate 10 μL of each of the following 2 solutions in methanol R: containing (A) 0.4 mg of the test substance per mL and (B) 0.4 mg of dacarbazine RS per mL. 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 (254 nm). The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to dacarbazine in the chromatogram obtained with solution (B).

Clarity and colour of solution. Dissolve 0.25 g of the test substance in a 210 g/L solution of citric acid R and dilute to 25.0 mL with the same solution. The solution is clear and not more intensely coloured than reference solution BY6, when analysed as described under 1.11.2 Degree of coloration of liquids, Method II.

[Note from the Secretariat. Chapter 1.11 Colour of liquids is currently under revision. Reference is already made to a new test procedure to be added under the section 1.11.2 Degree of coloration of liquids.]

Sulfated ash (2.3). Not more than 1.0 mg/g.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, method A. Use 1.00 g of the test substance. The water content is not more than 5 mg/g.

Impurity D

Carry out the test as described under 1.14.5 Gas chromatography with the apparatus equipped with an injection system for the performance of static head-space chromatography. Use a fused-silica capillary column 30 m long and 0.53 mm in internal diameter coated with base-deactivated polyethyleneglycol R (film thickness: 1.0 μm).

As a detector use a flame ionization detector.

Use helium for chromatography R as the carrier gas with a flow rate of 13 mL/min.

Use a split ratio of 1:1.

The following head-space injection conditions may be used:

- Equilibration temperature (°C): 60
- Equilibration time (min): 10
- Transfer line temperature (°C): 90
- Pressurization time (s): 30
- Injection volume (mL): 1
Maintain the temperature of the column at 35°C for 3 minutes, then raise the temperature within 8 minutes to 165°C, maintaining the temperature of the injection port at 180°C and that of the flame ionization detector at 220°C.

Prepare the following solutions. For solution (1) transfer 0.200 g of the test substance into a 20 mL headspace vial and firmly attach the septum and cap. Using a 10 µL syringe, inject 5 µL of water R into the vial. For solution (2) dilute 1.00 g of dimethylamine R (impurity D) to 100.0 mL with water R. Firmly attach the septum and cap to a 20 mL vial. Using a 10 µL syringe, inject 10 µL of solution (2) into the vial. For solution (3) dilute 1.00 g of trimethylamine R to 100.0 mL with water R. Firmly attach the septum and cap to a 20 mL vial. Using a 10 µL syringe, inject 10 µL of solution (2) and 10 µL of solution (3) into the vial.

Analyse solution (3). The test is not valid unless the resolution between the peaks due to impurity D and trimethylamine is at least 2.5.

Analyse solution (1) and (2).

In the chromatogram obtained with solution (1):

• the area of any peak corresponding to impurity D is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (0.05%).

**Related substances**

Use freshly prepared solutions and protect them from light.

• Perform test A and B.

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

Prepare the mobile phase by dissolving 15.63 g of docusate sodium R in a solution containing 2.33 g of glacial acetic acid R per L of water R and dilute to 1000 mL with the same solution. Prepare the mobile phase freshly every day and flush the column with a mixture of equal volumes of methanol R and water R after all tests have been completed or at the end of the day, for at least 2 hours.

Operate with a flow rate of 1.2 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

Prepare the following solutions in distilled water R. For solution (1) dissolve 50.0 mg of the test substance and 75 mg of citric acid R and dilute to 5.0 mL. For solution (2) dissolve 5.0 mg of dacarbazine impurity A RS and dilute to 50.0 mL. Dilute 5.0 mL of this solution to 25.0 mL.

Inject alternately 25 µL each of solution (1) and (2). Record the chromatograms for about 3 times the retention time of impurity A (retention time about 3 minutes).

In the chromatogram obtained with solution (1):

• the area of any peak corresponding to impurity A is not greater than the area of the corresponding peak in the chromatogram obtained with solution (2) (0.2%);
Dacarbazine (Ph. Int.)

- the area of any other impurity peak eluting after impurity A is not greater than 0.5 times the area of the peak due to impurity A in the chromatogram obtained with solution (2) (0.10%).

B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under test A with the following modifications.

Prepare the mobile phase by mixing 45 volumes of the mobile phase described under test A with 55 volumes of methanol R.

Prepare the following additional solution in distilled water R. For solution (3) dissolve 5.0 mg of dacarbazine impurity B RS, add 0.5 mL of solution (1) and dilute to 10.0 mL. Dilute 1.0 mL of this solution to 50.0 mL.

Inject alternately 10 μL each of solution (1) and (3). Record the chromatograms for about twice the retention time of dacarbazine (retention time about 12 minutes). The test is not valid unless the resolution between the peaks due to impurity B (with a relative retention of about 0.7) and dacarbazine is at least 1.5.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity B is not greater than the area of the corresponding peak in the chromatogram obtained with solution (3) (0.1%);
- the area of any other impurity peak is not greater than the area of the peak due to dacarbazine in the chromatogram obtained with solution (3) (0.10%);
- the sum of the areas of all impurities peaks is not greater than 5 times the area of the peak due to dacarbazine in the chromatogram obtained with solution (3) (0.5%). Disregard any peak with an area less than 0.5 times the area of the peak due to dacarbazine in the chromatogram obtained with solution (3) (0.05%).

Assay

- Protect the solutions from light throughout the assay.

Dissolve about 0.150 g, accurately weighed, in 30 mL of anhydrous acetic acid R. Titrate with perchloric acid (0.1 mol/L) VS, determining the end-point potentiometrically. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 18.22 mg of C₆H₁₀N₆O.

Impurities

A. 1,5-dihydro-4H-imidazo[4,5-P]-1,2,3-triazin-4-one (2-azahypoxanthine) (degradation product)
B. 5-amino-1H-imidazole-4-carboxamide (synthesis-related impurity)

[Note from the Secretariat. Chemical structure to be added.]

C. 5-diazenyl-1H-imidazole-4-carboxamide

[Note from the Secretariat. Chemical structure to be added.]

D. N-methylmethanamine

Reagents to be established

Water, distilled R
Water R prepared by distillation.

Polyethyleneglycol, base-deactivated R
Cross-linked, base-deactivated polyethyleneglycol, specially designed to be used as a stationary phase for gas chromatographic analysis of amine.
Replacement of mercury salts in non-aqueous titration

This is a draft proposal of a monograph for *The International Pharmacopoeia* (Working document QAS/17.708, July 2017). The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality_safety/quality_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).

**Note from the Secretariat.** As part of the activities to update *The International Pharmacopoeia*, mercury salts and other toxic reagents shall be replaced in order to reduce the risk to analysts and the environment. In the past, the addition of mercuric acetate has been necessary to permit the titration of halide salts of weak bases. These titrations can now be replaced by alternative procedures, notably the direct titration of the halide salts of weak bases with perchloric acid in anhydrous acetic acid or the titration of the halide salts of bases in alcoholic media with sodium hydroxide.

The general chapter 2.6. Non-aqueous titration was already revised following a decision at the 51st meeting of the Expert Committee on Specifications for Pharmaceutical Preparations. It is now proposed to revise individual monographs that prescribe the use of mercuric acetate in volumetric titration.

The proposed alternative procedures are predominantly based on provisions found in other pharmacopoeias; some of them are based on laboratory investigations.

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**Amiloride**

**Assay.** Dissolve about 0.45 g, accurately weighed, in a mixture of 100 mL of glacial acetic acid R1, 15 mL of dioxan R and 10 mL of mercuric acetate/acetic acid TS, and titrate with perchloric acid (0.1 mol/L) VS, determining the end-point potentiometrically as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 26.61 mg of $C_6H_8ClN_7O,HCl$.

**Assay.** Dissolve 0.20 g, accurately weighed, in a mixture of 5.0 mL of hydrochloric acid (0.01 mol/L) VS and 50 mL of dehydrated ethanol R. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. Read the volume added between the two points of inflexion. 1 mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 26.61 mg of $C_6H_8ClN_7O,HCl$. *(based on a method published in Ph.Eur. 9th Edition 2017)*

Continued
Amitriptyline hydrochloride  
**Assay.** Dissolve about 0.3 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of dioxan R and 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 31.39 mg of C_{20}H_{23}N.HCl.

**Assay.** Dissolve 0.25 g, accurately weighed, in 30 mL of dehydrated ethanol R. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. 1 mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 31.39 mg of C_{20}H_{23}N.HCl. [based on a method published in Ph.Eur. 9th Edition 2017]

Biperiden hydrochloride  
**Assay.** Dissolve about 0.4 g, accurately weighed, in 30 mL of glacial acetic acid R1, warming slightly to effect solution, add 10 mL of mercuric acetate/acetic acid TS and 0.15 mL of 1-naphtholbenzein/acetic acid TS as indicator. Titrate with perchloric acid (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 34.79 mg of C_{21}H_{29}NO.HCl.

**Assay.** Dissolve 0.20 g, accurately weighed, in 60 mL of dehydrated ethanol R. Carry out a potentiometric titration using potassium hydroxide/ethanol (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. 1 mL of potassium hydroxide/ethanol (0.1 mol/L) VS is equivalent to 34.79 mg of C_{21}H_{29}NO.HCl. [based on a method published in Ph.Eur. 9th Edition 2017]

Chlorhexidine dihydrochloride  
**Assay.** Dissolve about 0.4 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS, determining the end-point potentiometrically as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 14.46 mg of C_{22}H_{30}Cl_{2}N_{10}.2HCl.

**Assay.** In order to avoid overheating in the reaction medium, mix thoroughly throughout the titration and stop the titration immediately after the end-point has been reached. Dissolve 0.10 g, accurately weighed, in 5 mL of anhydrous formic acid R and add 70 mL of acetic anhydride R. Carry out a potentiometric titration using perchloric acid (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 14.46 mg of C_{22}H_{30}Cl_{2}N_{10}.2HCl. [based on a method published in Ph.Eur. 9th Edition 2017]

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Replacement of mercury salts in non-aqueous titration (Ph. Int.)

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**Chlorpromazine hydrochloride**

**Assay.** Dissolve about 0.7 g, accurately weighed, in 200 mL of acetone R, add 10 mL of mercuric acetate/acetic acid TS and 3 mL of methyl orange/acetone TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 35.53 mg of C_{17}H_{19}ClN_2S,HCl.

**Assay.** Dissolve 0.25 g, accurately weighed, in a mixture of 5.0 mL of hydrochloric acid (0.01 mol/L) VS and 50 mL of dehydrated ethanol R. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration, Method A. Read the volume added between the two points of inflexion. 1 mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 35.53 mg of C_{17}H_{19}ClN_2S,HCl. [based on a method published in Ph.Eur. 9th Edition 2017]

**Dopamine hydrochloride**

**Assay.** Dissolve about 0.4 g, accurately weighed, in 140 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 18.96 mg of C_8H_11NO_2,HCl.

**Assay.** In order to avoid overheating in the reaction medium, mix thoroughly throughout the titration and stop the titration immediately after the end-point has been reached. Dissolve 0.15 g, accurately weighed, in 10 mL of anhydrous formic acid R and add 50 mL of acetic anhydride R. Carry out a potentiometric titration using perchloric acid (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration, 1 mL of 0.1 M perchloric acid is equivalent to 18.96 mg of C_8H_11NO_2,HCl. [based on a method published in Ph.Eur. 9th Edition 2017]
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<td><strong>Edrophonium chloride</strong></td>
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<td><strong>Assay.</strong> Dissolve about 0.20 g, accurately weighed, in 20 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and 0.25 mL of quinaldine red/ethanol TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 20.17 mg of C\textsubscript{10}H\textsubscript{16}ClNO.</td>
<td><strong>Assay.</strong> In order to avoid overheating in the reaction medium, mix thoroughly throughout the titration and stop the titration immediately after the end-point has been reached. Dissolve 0.15 g, accurately weighed, in 60 mL of a mixture of equal volumes of acetic anhydride R and anhydrous acetic acid R. Carry out a potentiometric titration using perchloric acid (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. 1 mL of perchloric acid (0.1 mol/L) VS is equivalent to 20.17 mg of C\textsubscript{10}H\textsubscript{16}ClNO. [based on a method published in Ph.Eur. 9th Edition 2017]</td>
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| **Ephedrine hydrochloride** |  |
| **Assay.** Dissolve about 0.2 g, accurately weighed, in 10 mL of warm mercuric acetate/acetic acid TS, add 50 mL of acetone R and 1 mL of methyl orange/acetone TS as indicator and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 20.17 mg of C\textsubscript{16}H\textsubscript{15}NO,HCl. | **Assay.** Dissolve 0.15 g, accurately weighed, in 50 mL of dehydrated ethanol R and add 5.0 mL of hydrochloric acid (0.01 mol/L) VS. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. Read the volume added between the two points of inflexion. 1 mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 20.17 mg of C\textsubscript{16}H\textsubscript{15}NO,HCl. [based on a method published in Ph.Eur. 9th Edition 2017] |

| **Ethambutol hydrochloride** |  |
| **Assay.** Dissolve about 0.3 g, accurately weighed, in 100 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 13.86 mg of C\textsubscript{24}N\textsubscript{2}O\textsubscript{2},2HCl. | **Assay.** Dissolve 0.20 g, accurately weighed, in 50 mL of water R and add 1.0 mL of hydrochloric acid (0.1 mol/L) VS. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS. Read the volume added between the two points of inflexion. 1 mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 27.72 mg of C\textsubscript{24}N\textsubscript{2}O\textsubscript{2},2HCl. [based on a method published in Ph.Eur. 9th Edition 2017] |
Replacement of mercury salts in non-aqueous titration (Ph. Int.)

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<td><strong>Fluphenazine hydrochloride</strong></td>
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<td><strong>Assay.</strong> Dissolve about 0.5 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 25.52 mg of C$<em>{22}$H$</em>{26}$F$_3$N$_3$OS,2HCl.</td>
<td><strong>Assay.</strong> In order to avoid overheating during the titration, mix thoroughly throughout and stop the titration immediately after the end-point has been reached. Dissolve 0.22 g, accurately weighed, in a mixture of 10 mL of anhydrous formic acid R and 40 mL of acetic anhydride R. Carry out a potentiometric titration using perchloric acid (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. 1 mL of 0.1 M perchloric acid is equivalent to 25.52 mg of C$<em>{22}$H$</em>{26}$F$_3$N$_3$OS,2HCl. [based on a method published in Ph.Eur. 9th Edition 2017]</td>
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| **Homatropine hydrobromide** | |
| **Assay.** Dissolve about 0.3 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS, determining the end-point potentiometrically as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 35.63 mg of C$_{16}$H$_{21}$NO$_3$,HBr. | **Assay.** Dissolve 0.30 g, accurately weighed, in a mixture of 5.0 mL of hydrochloric acid (0.01 mol/L) VS and 50 mL of dehydrated ethanol R. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. Read the volume added between the two points of inflexion. 1 mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 35.63 mg of C$_{16}$H$_{21}$NO$_3$,HBr. [based on a method published in Ph.Eur. 9th Edition 2017] |

| **Homatropine methylbromide** | |
| **Assay.** Dissolve about 0.7 g, accurately weighed, in 50 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS, determining the end-point potentiometrically as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 37.03 mg of C$_{17}$H$_{24}$BrNO$_3$. | **Assay.** Dissolve 0.30 g, accurately weighed, in 10 mL of water R. Carry out a potentiometric titration using silver nitrate (0.1 mol/L) VS and a silver indicator electrode and a silver-silver chloride reference electrode. 1 mL of silver nitrate (0.1 mol/L) is equivalent to 37.03 mg of C$_{17}$H$_{24}$BrNO$_3$. [based on a method published in Ph.Eur. 9th Edition 2017] |
### Ketamine hydrochloride

**Assay.** Dissolve about 0.5 g, accurately weighed, in 1 mL of formic acid (~1080 g/L) TS and add 70 mL of a mixture of 6 volumes of acetic anhydride R and 1 volume of glacial acetic acid R1. Add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS, determining the end-point potentiometrically as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 27.42 mg of C\textsubscript{13}H\textsubscript{16}ClNO\textsubscript{2}HCl.

**Assay.** Dissolve 0.20 g, accurately weighed, in 50 mL of methanol R and add 1.0 mL of hydrochloric acid (0.1 mol/L) VS. Carry out a potentiometric titration, using sodium hydroxide (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. Read the volume added between the two points of inflexion.

1 mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 27.42 mg of C\textsubscript{13}H\textsubscript{16}ClNO\textsubscript{2}HCl. [based on a method published in Ph.Eur. 9th Edition 2017]

### Lidocaine hydrochloride

**Assay.** Dissolve about 0.55 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 27.08 mg of C\textsubscript{14}H\textsubscript{22}N\textsubscript{2}O\textsubscript{2}HCl.

**Assay.** Dissolve 0.22 g, accurately weighed, in 50 mL of dehydrated ethanol R and add 5.0 mL of hydrochloric acid (0.01 mol/L) VS. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. Read the volume added between the two points of inflexion.

1 mL of 0.1 M sodium hydroxide (0.1 mol/L) VS is equivalent to 27.08 mg of C\textsubscript{14}H\textsubscript{22}N\textsubscript{2}O\textsubscript{2}HCl. [based on a method published in Ph.Eur. 9th Edition 2017]

### Loperamide hydrochloride

**Assay.** Dissolve about 0.38 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and 0.15 mL of 1-naphtholbenzein/acetic acid TS as indicator and titrate with perchloric acid (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 51.35 mg of C\textsubscript{29}H\textsubscript{33}ClN\textsubscript{2}O\textsubscript{2}HCl.

**Assay.** Dissolve 0.40 g, accurately weighed, in 50 mL of dehydrated ethanol R and add 5.0 mL of hydrochloric acid (0.01 mol/L) VS. Carry out a potentiometric titration, using sodium hydroxide (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. Read the volume added between the two points of inflexion.

1 mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 51.35 mg of C\textsubscript{29}H\textsubscript{33}ClN\textsubscript{2}O\textsubscript{2}HCl. [based on a method published in Ph.Eur. 9th Edition 2017]

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**Replacement of mercury salts in non-aqueous titration (Ph. Int.)**

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**Continued**
Metoclopramide hydrochloride

**Assay.** Dissolve about 0.3 g, accurately weighed, in 80 mL of acetic anhydride R, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS, determining the end-point potentiometrically as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 33.63 mg of C\textsubscript{14}H\textsubscript{22}ClN\textsubscript{3}O\textsubscript{2}HCl.

Assay. Dissolve 0.25 g, accurately weighed, in a mixture of 5.0 mL of hydrochloric acid (0.01 mol/L) VS and 50 mL of dehydrated ethanol R. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. Read the volume added between the two points of inflexion.

1 mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 33.63 mg of C\textsubscript{14}H\textsubscript{22}ClN\textsubscript{3}O\textsubscript{2}HCl. [based on a method published in Ph.Eur. 9th Edition 2017]

Morphine hydrochloride

**Assay.** Dissolve about 0.3 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 32.18 mg of C\textsubscript{17}H\textsubscript{19}NO\textsubscript{3}HCl.

Assay. Dissolve 0.30 g, accurately weighed, in a mixture of 5 mL of hydrochloric acid (0.01 mol/L) VS and 30 mL of dehydrated ethanol R. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. Read the volume added between the two points of inflexion.

1 mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 32.18 mg of C\textsubscript{17}H\textsubscript{19}NO\textsubscript{3}HCl. [based on a method published in Ph.Eur. 9th Edition 2017]

Naloxone hydrochloride

**Assay.** Dissolve about 0.3 g, accurately weighed, in 40 mL of glacial acetic acid R1, add 10 mL of acetic anhydride R, 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 36.38 mg of C\textsubscript{19}H\textsubscript{21}NO\textsubscript{4}HCl.

Assay. Dissolve 0.30 g, accurately weighted, in 50 mL of dehydrated ethanol R and add 5.0 mL of hydrochloric acid (0.01 mol/L) VS. Carry out a potentiometric titration using sodium hydroxide/ethanol (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. Read the volume added between the two points of inflexion.

1 mL of sodium hydroxide/ethanol (0.1 mol/L) VS is equivalent to 36.38 mg of C\textsubscript{19}H\textsubscript{21}NO\textsubscript{4}HCl. [based on a method published in Ph.Eur. 9th Edition 2017]

Continued
Neostigmine bromide

**Assay.** Dissolve about 0.25 g, accurately weighed, in 20 mL of glacial acetic acid R1, add 5 mL of acetic anhydride R and 10 mL of mercuric acetate/acetic acid TS. Titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 30.32 mg of $C_{12}H_{19}BrN_2O_2$.

**Assay.** In order to avoid overheating in the reaction medium, mix thoroughly throughout the titration and stop the titration immediately after the end-point has been reached. Dissolve 0.23 g, accurately weighed, in 2 mL of anhydrous formic acid R and add 50 mL of acetic anhydride R. Carry out a potentiometric titration using perchloric acid (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. 1 mL of 0.1 M perchloric acid (0.1 mol/L) is equivalent to 30.32 mg of $C_{12}H_{19}BrN_2O_2$.

Pilocarpine hydrochloride

**Assay.** Dissolve about 0.5 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 24.47 mg of $C_{11}H_{16}N_2O_2.HCl$.

**Assay.** Dissolve 0.20 g, accurately weighed, in 50 mL of dehydrated ethanol R and add 5 mL of hydrochloric acid (0.01 mol/L) VS. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. Read the volume added between the two points of inflexion. 1 mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 24.47 mg of $C_{11}H_{16}N_2O_2.HCl$.

Procarbazine hydrochloride

**Assay.** Dissolve about 0.125 g, accurately weighed, in a mixture of 5 mL of formic acid (~1080 g/L) TS and 20 mL of glacial acetic acid R1, add 5 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 25.78 mg of $C_{12}H_{19}N_3O.HCl$.

**Assay.** Dissolve 0.2 g, accurately weighed, in 100 mL of water R. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS. 1 mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 25.78 mg of $C_{12}H_{19}N_3O.HCl$.
Replacement of mercury salts in non-aqueous titration (Ph. Int.)

Continued

<table>
<thead>
<tr>
<th>Current procedure</th>
<th>Alternative procedure</th>
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</table>

**Progananil hydrochloride**

**Assay.** Dissolve about 0.3 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/l) VS as described under 2.6 Non-aqueous titration, Method A, determining the end-point potentiometrically. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 14.51 mg of C<sub>11</sub>H<sub>16</sub>ClN<sub>5</sub>,HCl.

**Assay.** Suspend 0.10 g, accurately weighed, in 20 mL of anhydrous acetic acid R, shake and heat at 50°C for 5 minutes. Cool to room temperature and add 40 mL of acetic anhydride R. In order to avoid overheating in the reaction medium, mix thoroughly throughout the titration and stop the titration immediately after the end-point has been reached. Carry out a potentiometric titration using perchloric acid (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration.

1 mL of perchloric acid (0.1 mol/L) is equivalent to 14.51 mg of C<sub>11</sub>H<sub>16</sub>ClN<sub>5</sub>,HCl.


**Propranolol hydrochloride**

**Assay.** Dissolve about 0.6 g, accurately weighed, in 50 mL of glacial acetic acid R1 and add 10 mL of mercuric acetate/acetic acid TS, warming slightly if necessary to effect solution. Cool and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 29.58 mg of C<sub>16</sub>H<sub>21</sub>NO<sub>2</sub>,HCl.

**Assay.** Dissolve 0.25 g, accurately weighed, in 25 mL of dehydrated ethanol R. Carry out a potentiometric titration using 0.1 M sodium hydroxide (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration.

1 mL of 0.1 M sodium hydroxide (0.1 mol/L) is equivalent to 29.58 mg of C<sub>16</sub>H<sub>21</sub>NO<sub>2</sub>,HCl.

## Pyridostigmine bromide

**Assay.** Dissolve about 0.5 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and 2 drops of quinaldine red/ethanol TS as indicator and titrate with perchloric acid (0.1 mol/L) VS as described under **2.6 Non-aqueous titration**, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 26.11 mg of \( C_{9}H_{13}BrN_{2}O_{2} \).

**Assay.** In order to avoid overheating in the reaction medium, mix thoroughly throughout the titration and stop the titration immediately after the end-point has been reached. Dissolve 0.23 g, accurately weighed, in 10 mL of anhydrous acetic acid R and add 40 mL of acetic anhydride R. Carry out a potentiometric titration using perchloric acid (0.1 mol/L) VS, as described under **2.6 Non-aqueous titration**. 1 mL of perchloric acid (0.1 mol/L) is equivalent to 26.11 mg of \( C_{9}H_{13}BrN_{2}O_{2} \).


## Pyridoxine hydrochloride

**Assay.** Dissolve about 0.4 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS as described under **2.6 Non-aqueous titration**, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 20.56 mg of \( C_{8}H_{11}NO_{3},HCl \).

**Assay.** In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the end-point has been reached. Dissolve 0.15 g, accurately weighed, in 5 mL of anhydrous formic acid R. Add 50 mL of acetic anhydride R. Carry out a potentiometric titration using perchloric acid (0.1 mol/L) VS, as described under **2.6 Non-aqueous titration**. 1 mL of perchloric acid (0.1 mol/L) is equivalent to 20.56 mg of \( C_{8}H_{11}NO_{3},HCl \).


## Quinine dihydrochloride

**Assay.** Dissolve about 0.3 g, accurately weighed, in 50 mL of glacial acetic acid R1, add 20 mL of acetic anhydride R and 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS as described under **2.6 Non-aqueous titration**, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 19.87 mg of \( C_{20}H_{24}N_{2}O_{2},2HCl \).

**Assay.** Dissolve 0.15 g, accurately weighed, in 50 mL of dehydrated ethanol R and add 5.0 mL of 0.01 M hydrochloric acid. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS, as described under **2.6 Non-aqueous titration**. Read the volume added between the two inflexion points. 1 mL of 0.1 M sodium hydroxide (0.1 mol/L) VS is equivalent to 39.73 mg of \( C_{20}H_{24}N_{2}O_{2},2HCl \).

[Based on a proposal by a collaborating laboratory]

Continued
Replacement of mercury salts in non-aqueous titration (Ph. Int.)

Continued

<table>
<thead>
<tr>
<th>Current procedure</th>
<th>Alternative procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quinine hydrochloride</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Assay.</strong> Dissolve about 0.35 g, accurately weighed, in 50 mL of glacial acetic</td>
<td><strong>Assay.</strong> Dissolve 0.250 g, accurately weighed, in 50 mL of dehydrated ethanol R and</td>
</tr>
<tr>
<td>acid R1, add 20 mL of acetic anhydride R and 10 mL of mercuric acetate/acetic acid</td>
<td>add 5.0 mL of hydrochloric acid (0.01 mol/L) VS. Carry out a potentiometric titration</td>
</tr>
<tr>
<td>TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6</td>
<td>using sodium hydroxide (0.1 mol/L) VS. Read the volume added between the two inflexion</td>
</tr>
<tr>
<td>Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is</td>
<td>points. 1 mL of 0.1 M sodium hydroxide is equivalent to 36.09 mg of C_{14}H_{30}Cl_{2}N_{2}O_{4}.</td>
</tr>
<tr>
<td>equivalent to 18.04 mg of C_{20}H_{24}N_{2}O_{2},HCl.</td>
<td>[based on a method published in Ph.Eur. 9th Edition 2017]</td>
</tr>
<tr>
<td><strong>Suxamethonium chloride</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Assay.</strong> Dissolve about 0.3 g, accurately weighed, in 30 mL of glacial acetic</td>
<td><strong>Assay.</strong> In order to avoid overheating in the reaction medium, mix thoroughly</td>
</tr>
<tr>
<td>acid R1, add 30 mL of acetic anhydride R and 10 mL of mercuric acetate/acetic acid</td>
<td>throughout the titration and stop the titration immediately after the end-point has</td>
</tr>
<tr>
<td>TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6</td>
<td>been reached. Dissolve 0.15 g, accurately weighed, in 50 mL of acetic anhydride R.</td>
</tr>
<tr>
<td>Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is</td>
<td>Carry out a potentiometric titration using perchloric acid (0.1 mol/L) VS, as</td>
</tr>
<tr>
<td>equivalent to 18.07 mg of C_{14}H_{30}Cl_{2}N_{2}O_{4}.</td>
<td>described under 2.6 Non-aqueous titration.</td>
</tr>
<tr>
<td></td>
<td>1 mL of 0.1 M perchloric acid is equivalent to 18.07 mg of C_{14}H_{30}Cl_{2}N_{2}O_{4}.</td>
</tr>
<tr>
<td><strong>Tetracycline hydrochloride</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Assay</strong> A. Dissolve about 0.25 g, accurately weighed and previously dried at</td>
<td></td>
</tr>
<tr>
<td>60°C under reduced pressure, in 5 mL of formic acid (~1080 g/L) TS and 10 mL of</td>
<td>[Revision of the monograph will be dealt with in a separate document.]</td>
</tr>
<tr>
<td>glacial acetic acid R1, add 10 mL of dioxan R, 5 mL of mercuric acetate/acetic acid</td>
<td></td>
</tr>
<tr>
<td>TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6</td>
<td></td>
</tr>
<tr>
<td>Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is</td>
<td></td>
</tr>
<tr>
<td>equivalent to 48.09 mg of C_{22}H_{24}N_{2}O_{8},HCl.</td>
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</tr>
</tbody>
</table>
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Continued

Current procedure | Alternative procedure

**Thiamine hydrobromide**

**Assay.** Dissolve about 0.30 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 21.31 mg of C\textsubscript{12}H\textsubscript{17}BrN\textsubscript{4}OS, H\textsubscript{4}Br.

[Following discussions at the consultation on quality control laboratory controls and specifications for medicines, a proposal to omit the monograph from The International Pharmacopeia will be submitted to the Expert Committee on Specifications for Pharmaceutical Preparations.]

**Thiamine hydrochloride**

**Assay.** Dissolve about 0.25 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 16.86 mg of C\textsubscript{12}H\textsubscript{17}ClN\textsubscript{4}OS, HCl.

**Assay.** In order to avoid overheating in the reaction medium, mix thoroughly throughout the titration and stop the titration immediately after the end-point has been reached. Dissolve 0.11 g, accurately weighed, in 5 mL of anhydrous formic acid R and add 50 mL of acetic anhydride R. Carry out a potentiometric titration using perchloric acid (0.1 M) VS, as described 2.6 Non-aqueous titration. Perform the titration within 2 minutes and carry out a blank titration. 1 mL of perchloric acid (0.1 M) VS is equivalent to 16.86 mg of C\textsubscript{12}H\textsubscript{17}ClN\textsubscript{4}OS,HCl.

**Verapamil hydrochloride**

**Assay.** Dissolve about 0.5 g, accurately weighed, in 30 mL of glacial acetic acid R1, add 10 mL of mercuric acetate/acetic acid TS followed by 0.15 mL of 1-naphtholbenzein/acetic acid TS as indicator and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 Non-aqueous titration, Method A. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 49.11 mg of C\textsubscript{27}H\textsubscript{38}N\textsubscript{2}O\textsubscript{4}, HCl.

**Assay.** Dissolve 0.40 g, accurately weighed, in 50 mL of dehydrated ethanol R and add 5.0 mL of hydrochloric acid (0.01 mol/L) VS. Carry out a potentiometric titration using sodium hydroxide (0.1 mol/L) VS, as described under 2.6 Non-aqueous titration. Measure the volume added between the two points of inflexion. 1 mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 49.11 mg of C\textsubscript{27}H\textsubscript{38}N\textsubscript{2}O\textsubscript{4}, HCl.

Reagents to be established

Potassium hydroxide/ethanol (0.1 mol/L) VS

Potassium hydroxide R dissolved in ethanol (~710 g/L) TS to contain 5.61 g of KOH in 1000 mL.

**Method of standardization.** Ascertain the exact concentration of the solution following the method described under potassium hydroxide/ethanol (0.5 mol/L) VS.

Sodium hydroxide/ethanol (0.1 mol/L) VS

Sodium hydroxide R dissolved in ethanol (~710 g/L) TS to contain 4.00 g of NaOH in 1000 mL.

**Method of standardization.** Ascertain the exact concentration of the solution in the following manner:

Dissolve 0.10 g of benzoic acid R, accurately weighted, in 10 mL of water R and 40 mL of dehydrated ethanol R. Titrate with the sodium hydroxide/ethanol solution, determining the end-point potentiometrically or using 0.2 mL of thymolphthalein solution R as indicator. Standardize immediately before use.

1 mL of 0.1 M sodium hydroxide/ethanol (0.1 mol/L) VS is equivalent to 12.21 mg of $\text{C}_7\text{H}_6\text{O}_2^-$. 

***
Polymorphism

This is a draft proposal of a monograph for *The International Pharmacopoeia* (Working document QAS/17.716, July 2017). 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 publish the following chapter on Polymorphism in the Supplementary Information section under “Notes for guidance”.*

Active pharmaceutical ingredients (APIs) and excipients, in the solid phase, can be classified as either crystalline or amorphous solids or a mixture thereof. A crystalline structure implies that the structural units (*i.e.* unit cells) are repeated regularly, indefinitely and three-dimensionally in space. The unit cells of an amorphous solid, however, are arranged in a non-ordered, random system, related to the liquid state.

**Polymorphism** is the phenomenon where crystalline forms of the same chemical compound exist in different crystalline phases. The difference in internal crystal structure could be attributed to differences in crystal packing arrangements and/or different molecular conformations. When a chemical element exists in different crystalline forms, it is referred to as **allotropy**, not polymorphism (1). The phenomenon where crystals with the same internal structure exhibit different external shapes is referred to as **crystal habit**.

Other variations in the crystal structures of the same chemical compound are encountered where these unit cells differ in elemental composition through the inclusion of one or more solvent molecules, known as **solvates**. Solvent inclusion can be in stoichiometric or non-stoichiometric order. In the past solvent inclusion has been considered to be a mechanism of polymorphism (due to changes/differences in the unit cell of a solid) but was dubbed **pseudopolymorphism**, due to the fact that the composition of the pseudopolymorph differs chemically (due to the presence of solvent molecules) from the unsolvated form. The terms **solvatomorphs** and **solvatomorphism** are also used to avoid issues associated with inconsistent nomenclature (2).

When water is incorporated in stoichiometric proportions into the crystal lattice of the compound, the molecular adduct(s) formed is referred to as a **hydrate**.

Occasionally a compound of a given hydration/solvation state may crystallize into more than one crystalline form, thus producing hydrates/solvates that exhibit polymorphism themselves, which is known as **polymorphic pseudopolymorphs**. An example of this phenomenon is nitrofurantoin (3). Nitrofurantoin can be crystallized as two monohydrated forms (Forms I and II) and two anhydrous species (designated polymorphs α and β) (3). Solvated forms (from different solvents) that do not exhibit significant differences in XRPD patterns and crystal packing (*e.g.* hydrate and isopropanolate of hexakis(2,3,6-tri-O-acetyl)-α-cyclodextrin) are called **isostructural pseudopolymorphs** (4).
The term *desolvated solvates* has been used to classify a compound that was originally crystallized as a solvate but when the incorporated solvent is removed the crystal lattice of the solvated and desolvated crystal lattices do not show any or relatively small differences, for example, desolvated monohydrate of terazosin HCl (5).

Amorphous forms of APIs and excipients are of substantial interest because they are usually more soluble than their crystalline counterparts but are usually considered to be thermodynamically less stable. Solid-state properties of amorphous forms of the same chemical compound (*i.e.* melting behaviour, solubility profile, etc.) may differ; this phenomenon is referred to as *polyamorphism* (6).

Another phenomenon of crystal engineering is that of *pharmaceutical co-crystals*. *Pharmaceutical co-crystals* can be defined as crystalline materials comprised of an API and one or more unique co-crystal formers (e.g. fluoxetine HCl/succinic acid co-crystal), which are solids at room temperature (7), thus it is suggested that co-crystal formation could be considered a subdivision of pseudopolymorphism.

Variation in the crystallization conditions (temperature, pressure, solvent, concentration, rate of crystallization, seeding of the crystallization medium, presence and concentration of impurities, etc.) may cause the formation of different crystalline forms and/or solvates. In general, the more stable the form (including polymorphs, amorphous forms, etc.), the less soluble the form is in water.

*Figure 1* provides a summary of the groups wherein solids can be classified.

Crystalline forms are characterized based on the differences of their physical properties. *Table 1* lists some examples of the properties that may differ among different morphic forms (9).

**Table 1. Examples of physical properties that may differ among different morphic forms** (9)

<table>
<thead>
<tr>
<th>1. Packing properties</th>
<th>3. Spectroscopic properties</th>
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</thead>
<tbody>
<tr>
<td>a. Molar volume and density</td>
<td>a. Vibrational transitions (<em>i.e.</em> infrared absorption spectra and Raman spectra)</td>
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<tr>
<td>b. Refractive index</td>
<td>b. Rotational transitions (<em>i.e.</em> far infrared or microwave absorption spectra)</td>
</tr>
<tr>
<td>c. Conductivity (electrical and thermal)</td>
<td>c. Nuclear spin transitions (<em>i.e.</em> solid state nuclear magnetic resonance spectra)</td>
</tr>
<tr>
<td>d. Hygroscopicity</td>
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<tr>
<td>2. Thermodynamic properties</td>
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</tr>
<tr>
<td>a. Melting and sublimation temperatures</td>
<td></td>
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<tr>
<td>b. Internal energy (<em>i.e.</em> structural energy)</td>
<td></td>
</tr>
<tr>
<td>c. Enthalpy (<em>i.e.</em> heat content)</td>
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<tr>
<td>d. Heat capacity</td>
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<tr>
<td>e. Entropy</td>
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<tr>
<td>f. Free energy and chemical potential</td>
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<tr>
<td>g. Thermodynamic activity</td>
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<tr>
<td>h. Vapour pressure</td>
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<tr>
<td>i. Solubility</td>
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<tr>
<td>4. Kinetic properties</td>
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<tr>
<td>a. Dissolution rate</td>
<td></td>
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<tr>
<td>b. Rates of solid state reactions</td>
<td></td>
</tr>
<tr>
<td>c. Stability</td>
<td></td>
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<tr>
<td>5. Surface properties</td>
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<tr>
<td>a. Surface-free energy</td>
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<tr>
<td>b. Interfacial tensions</td>
<td></td>
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<tr>
<td>c. Habit (<em>i.e.</em> shape)</td>
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</tr>
<tr>
<td>6. Mechanical properties</td>
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</tr>
<tr>
<td>a. Hardness</td>
<td></td>
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<tr>
<td>b. Tensile strength</td>
<td></td>
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<tr>
<td>c. Compatibility, tableting</td>
<td></td>
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<tr>
<td>d. Handling, flow, and blending</td>
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</tbody>
</table>
Table 2 summarizes some of the most commonly used techniques to study and/or classify different morphic forms of substances. These techniques are often complementary and it is indispensable to use several of them.

Any method(s) chosen to confirm the identity of the specific form(s) must be validated to show the method is suitably specific for the identification of the desired form(s).
Table 2. Examples of some techniques that may be used to study and/or classify different crystalline forms of substances

1. X-ray powder diffraction
2. Single crystal X-ray diffraction
3. Microcalorimetry
4. Thermal analysis (1.2.1 Melting point,* differential scanning calorimetry, thermogravimetry, thermomicroscopy)
5. Moisture sorption analysis
6. Microscopy (electronic and optical)
7. Solid-state nuclear magnetic resonance;
8. Solubility studies
9. Spectrophotometry in the infrared region (1.7)*
10. Intrinsic dissolution rate
11. Density measurement

* Methods employed by The International Pharmacopoeia

When a substance shows polymorphism the form with the lowest enthalpy at a given temperature and pressure is the most thermodynamically stable. The other forms are said to be in a metastable state. At normal temperature and pressure a metastable form may remain unchanged or may change to a thermodynamically more stable form.

Polymorphism, amorphism and pseudopolymorphism (or solvatomorphism) of APIs and excipients are of interest, as they may affect the bioavailability, suitability for manufacturing of solid dosage forms and thermodynamic stability of the polymorphic form included in the solid dosage form. Control of the morphic form by the manufacturer is necessary during the processing of APIs and excipients and during the manufacturing of a dosage form to ensure the correct physical characteristics thereof. The control of a specific morph is especially critical in the areas where the bioavailability and stability are directly impacted.

The morphic form of a readily soluble starting material that is incorporated into a solution, for example, an injection, an oral solution or eye drops, is normally non-critical (an exception to this statement might be if the concentration of the solution is such that it is close to the limit of solubility of one of the possible polymorphs). Similarly, if the API is processed during the manufacturing process to obtain an amorphous form (e.g. hot melt extrusion), the original form is considered non-critical.

The morphic form may be critical when the material is included in a solid dosage form or as a suspension in a liquid dosage form when the characteristics of the different polymorphs are such as to affect the bioavailability or dissolution of the material (10). The polymorphic form of a biopharmaceutical classification system (BCS) class I or III API in a solid oral dosage form is normally non-critical in terms of dissolution rate or bioavailability.

The inclusion of potentially harmful solvents in the crystal lattice which may render APIs or excipients to be toxic or harmful to patients (i.e. solvates) should also be suitably regulated and monitored by the manufacturer.
Where a monograph indicates that a substance shows polymorphism this may be true crystal polymorphism, occurrence of solvates, allotropy or occurrence of the amorphous form. Due to the identical chemical composition of the polymorphic substance it will have the same chemical behaviour in solution, irrespective in the form in which it is presented.

The International Pharmacopoeia controls the morphic forms of a limited number of substances by restricting it to either:

- a single form, for example, Carbamazepine API (Anhydrous Form III), Mebendazole API (Form C); or
- by limiting the presence of unwanted morphic forms, for example, Chloramphenicol palmitate API (should contain at least 90% of polymorph B).

The control of morphic forms may be achieved by:

- permitting no deviation from the infrared absorption spectrum of the reference substance prescribed (or reference spectrum supplied) – when the infrared absorption spectrum has been validated to be specific to the preferred form and able to distinguish the undesired form(s), for example, Indomethacin API;
- restricting the melting point range, for example, Phenobarbital API;
- recommending the use of any other suitable methods such as X-ray powder diffractometry, for example, Carbamazepine tablets;
- limiting the incorporated solvent (in the case of solvatomorphs) with a specific limit test, for example, Nevirapine hemihydrate API.

In the instance where polymorphism may be present the user will be able to deduce this from the infrared identification test (if infrared spectrophotometry is suitable for the detection of differences in morphic forms of the specific compound) where the user may be instructed to:

- recrystallize both the test substance and the specified reference substance, in the event where the infrared spectra are found to be not concordant, for example, Fluconazole API; and/or
- dry the API and/or specified reference substance to ensure that both forms are in the anhydrous or dehydrated state, for example, Nevirapine hemihydrate API.

In the event where the choice of a specific morphic form is critical with regard to bioavailability and/or stability, the method of the manufacture of the product should ensure the presence of desired polymorph in the final product. The Secretariat will include a statement under the heading “Manufacturing” to draw attention to the control of a specified morphic form during manufacture where control is known to be critical, for example, Carbamazepine oral suspension.

It is the intention of The International Pharmacopoeia to extend the inclusion of explicit statements in monographs, where appropriate, as information on the occurrence of polymorphism becomes available. The Secretariat thus cordially invites the users of The International Pharmacopoeia and manufacturers to share such information that could be included in the monographs if considered being appropriate.
Bibliography


***
1. Introduction and background

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has been undergoing structural changes and its membership has changed. For details please see the following website: http://www.ich.org/about/organisational-changes.html

In view of these changes a need was identified for the definition for a “stringent regulatory authority” (SRA) to be reviewed since it is directly linked to ICH membership.

The definition used in World Health Organization (WHO) guidance texts prior to the organization changes in ICH reads as follows:

“A regulatory authority which is:

a. a member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (as specified on www.ich.org); or

b. an ICH observer, being the European Free Trade Association (EFTA), as represented by Swissmedic and Health Canada (as may be updated from time to time); or

c. a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time). “


The term (and definition) for SRA is currently used in the following guidelines in the context of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP):
Proposal for updating the definition of “stringent regulatory authority”

- Procedure for prequalification of pharmaceutical products.  
  (Annex 10, 45th ECSPP report, TRS 941, 2011)
- Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part  
  (Annex 4, 46th ECSPP report, TRS 970, 2012)
- Pharmaceutical development of multisource (generic) finished pharmaceutical products - points to consider
  (Annex 3, 46th ECSPP report, TRS 970, 2012)
- WHO guidelines on variations to a prequalified product  
  (Annex 3, 47th ECSPP report, TRS 981, 2013)
- Model quality assurance system for procurement agencies
  (Annex 3, 48th ECSPP report, TRS 986, 2014)
- Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities
  (Annex 5, 48th ECSPP report, TRS 986, 2014)
- Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part
  (Annex 6, 48th ECSPP report, TRS 986, 2014)
- Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products
  (Annex 8, 49th ECSPP report, TRS 992, 2015)
- List of International Comparator Pharmaceutical Products and related Notes
  (Update 2016)

(References:
  (link: http://www.who.int/medicines/services/expertcommittees/pharmprep/20160302_QASterminologyDB.pdf?ua=1); and
(2) WHO ECSPP guidelines and guidance, website (link: http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/)

2. Interim definition

Based on the latest definition published at the time of the meeting, the members of the 51st ECSPP discussed the need for revision and the resulting deliberations in their report read as follows (TRS 1003):
“Definition of stringent regulatory authority

The WHO prequalification procedure and several other WHO guidance documents provide for mechanisms to rely on SRAs, defining an SRA as a regulatory authority which is a member or an observer of ICH, or is associated with an ICH member through a legally-binding mutual recognition agreement. The definition originated from the Global Fund and it is reflected in the quality assurance policies of most major international organizations involved in procuring medicines.

ICH has undergone structural changes and has expanded its reach to include organizations and associations at the global level. In view of these developments the WHO Secretariat proposed an interim definition of an SRA. The interim definition of an SRA will include the same elements as the current definition, each qualified by the wording `as before 23 October 2015’, as follows:

A regulatory authority which is:

- a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); or
- an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or
- a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015).’

The Expert Committee adopted the interim definition and noted the work being done towards developing a new approach to the assessment of national regulatory authorities, based on the various existing systems currently in place such as that used by the Pan American Health Organization and that applied by WHO with respect to vaccines. The Committee requested that an update on this work be provided at its fifty-second meeting.

3. Proposal

As a follow-up action, internal discussions have taken place within the WHO Regulation of Medicines and other Health Technologies unit towards the development of a new proposal in reply to the ECSPP recommendations. Please find herewith the elements for a new concept that have come out of these discussions.

One governing principle discussed was that the definition and criteria should be acceptable to Member States, agencies that use this definition, such as international procurement agencies, and WHO.
Proposal for updating the definition of “stringent regulatory authority”

Moreover, the criteria/principle to be used for establishing effective performance, confidence/trust (and the process to build these) are part of the WHO Global Benchmarking Tool (GBT) maturity level (ML) 4 assessments of national regulatory authorities (NRAs). The GBT, including ML 4 requirements and assessment process, are being discussed for endorsement by Member States. The GBT will be used to assess medicines, vaccines, blood and blood products and medical devices, including in vitro diagnostics.

Based on the above, it is proposed that the definition for stringent regulatory authority (SRA) could be replaced by the following concept for NRAs to be “on the list”, i.e. qualify as “XXX”, including:

1. grandfathering NRAs identified as “SRAs” in accordance with the current interim definition;
2. need for transparent process for expansion to additional NRAs: the results and basis should be publicly available to be utilizable;
3. use of the GBT ML 4 assessment and risk-based re-assessment as criteria for adding and maintaining NRAs “on the list”;
4. modular approach to enable NRAs to be “on the list” for a specific function and/or product group.

A new term and abbreviation for “SRAs”, “XXX”, will need to be determined. Therefore, we seek your input on proposals for the new term to replace the current “stringent regulatory authority” term and the abbreviation “SRA”, and proposed definition for the new term taking into account the main principles and concepts noted in the previous paragraphs in this document.

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Other draft guidelines

The following medicines quality-related guidelines have been posted for public comment on the WHO website. The working documents with line numbers are available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

- **Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products**
  **Working document QAS/15.639/Rev.2 (July 2017)**
  These guidelines focus primarily on good manufacturing practice (GMP) for the design, qualification, management and maintenance of heating, ventilation and air-conditioning (HVAC) systems in facilities manufacturing non-sterile dosage forms. The text should be read together with the parent WHO guideline on GMP (Annex 2 to WHO Technical Report Series 986, 2014). Additional requirements for air-handling systems of pharmaceutical hazardous, sterile and biological products are covered in separate WHO guidelines. The proposed text is a revision of the 2011 guidelines (Annex 5 to WHO Technical Report Series 961) and sets out recommended standards in line with current technical and regulatory approaches. The illustrative examples included in the 2011 text have been removed from the revised text and will be provided in a separate document in the future.

- **Stability testing of active pharmaceutical ingredients and finished pharmaceutical products**
  These guidelines seek to exemplify the core stability data package required for registration of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), replacing the previous WHO guidelines in this area. However, alternative approaches can be used when they are scientifically justified. Further guidance can be found in relevant ICH and WHO guidelines. It is recommended that these guidelines should also be applied to products that are already being marketed, e.g. upon re-registration or re-evaluation. The guidelines do not apply to biological products.

- **Facilitated registration of stringently approved medicines and vaccines**
  (Full title:) Facilitated procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (SRAs)
  This is a revision of the draft text proposing a scheme to facilitate accelerated national registration of medicines and vaccines approved by stringent regulatory authorities.
• **WHO draft guidance on testing of “suspect” falsified medicines**
  Working document QAS/15.634/Rev.3 (August 2017)
  This document provides technical guidance on laboratory testing of samples of suspected falsified products detected on the markets of WHO Member States and related aspects of sampling and reporting.

• **Good practices for desk assessment**
  (Full title:) *Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions*
  Inspection of manufacturing, testing, clinical trial and distribution sites poses an increasing burden on regulatory authorities. It is therefore good practice to rely on inspection information from other trusted authorities as part of risk-based inspection planning, so that there is no on-site inspection without well-founded cause. This text aims to provide general guidance on performing desk assessments in lieu of onsite inspections.

• **Draft notes on the conduct of solubility studies**
  The objective of this document is to provide some guidance on the design and conduct of solubility studies undertaken for the purpose of active pharmaceutical ingredient (API) classification within the Biopharmaceutics Classification System (BCS).