## 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)
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)
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

Regulating medicine manufacturers: is an on-site inspection the only option?

The Australian approach to meeting inspection demands

On-site inspections of manufacturing and testing sites for medicines are resource-intensive for both regulators and manufacturers, especially as an increasing number of sites are located outside regulatory authorities' territories. To maximize the impact of limited resources, it is therefore good regulatory practice to leverage available evidence from other agencies as part of a risk-based inspection planning process.

The Australian Department of Health's Therapeutic Goods Administration (TGA) has been using a risk- and reliance-based approach in inspection planning for some time. This article describes the TGA's pathways for granting good manufacturing practice (GMP) clearance.

Background
A cornerstone of effective medicine regulation is ensuring that the medicines available within a market meet appropriate quality standards. To this end, a national regulatory authority (NRA) will assess product quality data during pre-market assessment. Generally, this involves assessment of quality data provided as part of the application dossier (1) by the applicant, and an onsite inspection of the product manufacturer against compliance with the applicable Good Manufacturing Practice (GMP) standards, such as those developed by WHO and used in its Prequalification Programme (2,3) or those of the Pharmaceutical Inspection Convention/Pic/S (4).

Where the manufacturer has been previously inspected and approved by the NRA, an onsite assessment may be avoided if the manufacturing steps are the same. If the product is approved for supply, the NRA monitors the manufacturer's compliance with applicable GMP standards via regular inspections, either announced or unannounced.

A key objective of a GMP inspections programme is to provide the NRA with a proactive mechanism for identifying and preventing quality related medicine safety risks. Once a manufacturer is approved for supplying medicines to the market, re-inspections are usually conducted.

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within a risk framework that takes into account product and process risks and manufacturer compliance history.\textit{(e.g. 5,6)} The objective should be to conduct more frequent inspections of manufacturers with a higher risk profile. In contrast, where a manufacturer has demonstrated a high level of voluntary compliance with GMP standards over time, re-inspections could be conducted on a less frequent basis.

**Challenges in meeting demand for GMP inspections**
Maintaining an effective GMP inspections programme can be challenging for many reasons, including the following:

**Availability of appropriately trained and qualified staff**
Given the technical nature of the work involved in planning, conducting and closing out GMP inspections, GMP inspectors must have appropriate academic qualifications and professional experience.

Factors that may impact on an NRA’s ability to build and maintain a team of appropriately experienced GMP inspectors include the presence of a domestic manufacturing industry, tertiary education institutions that offer suitable courses and the ability of a regulator to offer salaries that are competitive with those offered by industry.

**Inspecting international manufacturers**
Depending on the size and diversity of the domestic pharmaceutical market, NRAs may need to regulate a large number of domestic and/or overseas pharmaceutical manufacturers. In some countries, including Australia, there are many more international manufacturers than domestic manufacturers supplying the market.

Challenges associated with inspecting international manufacturers include travel costs and logistics, visa and other entry requirements, language barriers and inspector health and security risks.

**Demand for inspections outstrips capacity**
As the pharmaceutical supply chain becomes more complicated, the demand for GMP inspections can exceed the capacity of an NRA to meet that demand. In particular, with the emergence of contract manufacturing, multiple manufacturing sites may be associated with a single product. This can be mitigated to some extent by relying on the supplier qualification processes of the finished dosage form manufacturer.

Nevertheless, with increasing investment by international pharmaceutical companies in emerging medicine manufacturing economies, it is likely that the demand for GMP inspections will increase over time.

**Consequences of not meeting demand for GMP inspections**
The consequences of insufficient resources being available to meet the demand for GMP inspections include:

**Delayed access to new medicines by patients**
Delays in inspecting new manufacturers, or new manufacturing steps conducted by previously approved manufacturers, may delay product approvals. This may delay access of patients to new or essential medicines, which in turn may adversely impact on public health programmes.

**Reduced ability of the NRA to identify and manage medicine quality risks**
Failure to conduct GMP inspections within risk-based re-inspection timeframes reduces
the NRA’s ability to identify manufacturing failures that may affect the safety profile of medicines. This increases the risk that patients may be exposed to medicines that do not meet applicable specifications and quality standards. Such medicines pose a risk to consumers as they may not achieve the desired health outcomes. Further, in the case of medicines used to treat infectious diseases, substandard medicines may promote the emergence of resistant strains of the infectious agent.

Lengthy approval times may deter investments and imports
Delays in approval times may be a disincentive for foreign investors to build manufacturing capacity in target countries. It may also be a disincentive for local distributors to apply for permits to import and supply medicines made by international manufacturers. This in turn may limit access to medicines that patients need.

Meeting the challenge: The Australian approach
The Australian Department of Health’s TGA is responsible for regulating the supply, import, export, manufacturing and advertising of therapeutic goods in Australia.

Under Australian law an applicant seeking pre-market approval of a medicinal product must supply evidence demonstrating that each manufacturer involved in the manufacture of the product has acceptable manufacturing and quality control procedures in place. It is also a condition of ongoing product approval that such evidence is supplied on request.

The TGA conducts GMP inspections of all Australian manufacturers of medicines. For manufacturers located outside of Australia, the applicant must obtain a TGA GMP clearance for each site, that specifies which manufacturing steps for the required dosage forms can be undertaken.

TGA conducts 80–120 inspections of international manufacturers and about 150–200 inspections of Australian manufacturers every year. However, the Agency does not have the resources to maintain a regular inspection programme for every international manufacturer that supplies API and/or finished product to the Australian market. The TGA has developed a risk-based desktop assessment process that relies on information from recognized regulators. This process has reduced the number of overseas on-site inspections to be performed.(7)

There are two types of desk top assessments that TGA conducts to make a decision about whether to issue a TGA GMP clearance to the international manufacturer:

Mutual Recognition Agreement Pathway
The TGA accepts GMP Certificates issued by a country with which Australia has a Mutual Recognition Agreement (MRA), based on an inspection within their own borders. Evaluation under the MRA pathway includes an assessment of a current GMP Certificate to identify the manufacturing site, to ensure an equivalent GMP standard is applied, and to verify that the scope (manufacturing steps and dosage forms) is relevant to the product to be supplied in Australia.

Compliance Verification Pathway
TGA may also accept evidence from the following:
• An MRA regulatory authority, for inspections performed outside their own borders; or
• the U. S. FDA, for inspections performed inside or outside its own border; or
Australian approach to meeting inspection demands

Table 1 – Evidence required for Compliance Verification Assessments

<table>
<thead>
<tr>
<th>All non-sterile dosage forms &amp; APIs</th>
<th>Sterile and Biotech APIs and Sterile Dosage forms</th>
<th>Contract Testing Laboratories and Contract Sterilizers</th>
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<tbody>
<tr>
<td>Current GMP Certificate</td>
<td>Current GMP Certificate</td>
<td>Current GMP Certificate</td>
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<tr>
<td>A list of all regulatory inspections conducted within the past 3 years, and a copy of the most recent inspection report</td>
<td>A list of all regulatory inspections conducted within the past 3 years, and a copy of the most recent inspection report</td>
<td>A list of all regulatory inspections conducted within the past 3 years, and a copy of the most recent inspection report</td>
</tr>
<tr>
<td>Details of any regulatory actions in the past 3 years</td>
<td>Details of any regulatory actions in the past 3 years</td>
<td>Details of any regulatory actions in the past 3 years</td>
</tr>
<tr>
<td>Site Master File, Quality Manual or equivalent</td>
<td>Site Master File, Quality Manual or equivalent</td>
<td>Quality Manual / Laboratory Manual or equivalent</td>
</tr>
<tr>
<td>GMP agreement between the sponsor and the manufacturer(a)</td>
<td>GMP agreement between the sponsor and the manufacturer(a)</td>
<td>GMP agreement between the sponsor and the contract test laboratory or sterilizer(b)</td>
</tr>
<tr>
<td>List of products intended for supply in Australia</td>
<td>List of products intended for supply in Australia</td>
<td>A list of tests a laboratory is authorized to perform</td>
</tr>
<tr>
<td>Copy of the procedures for release for supply of products included in the Clearance application(a)</td>
<td>Copy of the procedures for release for supply of products included in the Clearance application</td>
<td>For botanical ingredients, evidence that authenticated standard reference materials are used</td>
</tr>
<tr>
<td>Validation Master Plan</td>
<td></td>
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<tr>
<td>Latest Product Quality Review</td>
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(a) not required unless requested

(b) or principal manufacturer and laboratory/sterilizer

- a recognized regulatory authority of a country with which Australia does not have an MRA (e.g. PIC/S members¹), for inspections performed within their own borders.

This pathway requires additional data to be supplied by the applicant (Table 1). A Compliance Verification assessment includes a detailed assessment of a recent GMP certificate and an inspection report prepared by an overseas regulatory agency recognized by the TGA, together with supporting manufacturing documentation supplied by the applicant or international manufacturer. The extent of the assessment process depends on the regulatory evidence required and increases with product risk and the complexity of manufacture.

The MRA and Compliance Verification assessments may result in a TGA decision to:
- issue a GMP Clearance, valid for a specified period, based on the date of the last on-site inspection performed by the recognized regulator;
- issue a GMP Clearance, valid for a specified period but with one or more conditions; or
- not issue a GMP Clearance where the evidence does not support the scope of the GMP Clearance application.

¹ https://www.picscheme.org/en/members
TGA currently has MRA (or equivalent arrangements) with the European Union and several other jurisdictions covering 29 countries, and recognizes evidence from an additional 17 regulatory authorities.

Where there is no suitable evidence available from a recognized regulator to support a GMP Clearance application, the TGA will perform an onsite inspection of the international manufacturing site. The TGA always reserves the right to inspect an international manufacturing site regardless of what other evidence is available, particularly if issues have been identified during the compliance verification assessment or if there are concerns about the site's GMP compliance.

Conclusions
The TGA's GMP clearance system was created in the early 2000s to facilitate the efficient and effective management of the Agency's regulatory compliance programmes and reduce the regulatory burden on industry. The widespread use of GMP clearances has significantly reduced the number of overseas TGA inspections required. The Agency is also undertaking an increasing number of joint inspections with other regulators and is contributing to the development of information-sharing mechanisms through the International Coalition of Medicines Regulatory Authorities (ICMRA). These initiatives are consistent with the principle adopted by the Australian Government that “if a system, service or product has been adopted under a trusted international standard or risk assessment, no additional requirements should be imposed for approval in Australia, unless it can be demonstrated that there is a good reason to do so”. This principle of regulatory reliance is today more relevant than ever.

References
5 PIC/S. A recommended model for risk-based inspection planning in the GMP environment. PI 037-1. 1 January 2012.
7 TGA. Australian Regulatory Guidelines. Good Manufacturing Practice (GMP) clearance for overseas manufacturers.

2 http://www.icmra.info
Placebo and drug kits in clinical trial design

New and improved medicinal products are continuously needed throughout the world to prevent and treat diseases. Good quality clinical trials are key in bringing new safe and effective medicines to patients. Some information is outlined below on specific aspects of conducting clinical studies, namely the use of placebo as a control intervention and the use of drug kits for effective blinding of trials.

Introduction

Before novel medicinal products are introduced into widespread use, they must be assessed in clinical trials. Randomized controlled trials (RCTs) are often considered the gold standard in this regard, although other study designs can also yield valid research results. Clinical trials should be designed in such a way that the effects of the experimental intervention are compared with those of a control intervention. In a controlled trial, the subjects in the study and control group should be drawn from the same population, and should preferably be assigned to the groups by randomization to remove bias in the allocation of participants. Where feasible, clinical trials should be blinded, so that the subjects – and in double-blinded studies also the researchers – are unaware of who is receiving which intervention. This helps to avoid behaviour changes that may influence the study outcomes. (1)

Two questions are discussed below that commonly arise in developing and evaluating clinical trial designs, namely in what situations it is acceptable to use placebo in the control arm, and how to achieve effective blinding.

The use of placebo

A placebo has been defined as “an inert substance or sham procedure that is provided to research participants with the aim of making it impossible for them, and usually the researchers themselves, to know who is receiving an active or inactive intervention.” (1)

Placebos typically consist of the ingredients employed in the medicinal product under study minus the active ingredient, making them inert. The inactive ingredients (excipients) employed in a pharmaceutical product must be “generally recognized as safe” (1) for use in humans, otherwise a medicinal product would not be authorized for use.

In vaccine research, the term “placebo” is also applied to non-inert substances. In this context, an existing vaccine not studied in the trial is added to both the investigational and the control product in order to avoid giving an “empty” injection to the subjects in the control group. A disadvantage of this approach is that it complicates the

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1 The U.S. Food, Drug, and Cosmetic Act makes provision for food additives to be shown to be “Generally Recognized As Safe” (GRAS) through scientific procedures. Similar approaches are used in other jurisdictions.

This article originates from a request for advice sent to the WHO Prequalification Team. We thank Dr Matthias Stahl for his technical input. The article outlines selected concepts as found in published literature. It should not be considered as WHO guidance on the subject.
evaluation of the safety and reactogenicity of the vaccine under study.\(^{(2)}\)
As the risks associated with the placebo product are typically very low or non-existent, the use of placebos is generally uncontroversial where there is no established effective intervention for the issue being researched. Where an established effective intervention exists, on the other hand, the use of placebo often raises controversy among members of research ethics committees (RECs), regulators, and policy-makers. The CIOMS Guideline 5, *Choice of control in clinical trials*, advises as follows:

“As a general rule, the research ethics committee must ensure that research participants in the control group of a trial of a diagnostic, therapeutic, or preventive intervention receive an established effective intervention. Placebo may be used as a comparator without providing the established effective intervention to participants only if:

- there are compelling scientific reasons for using placebo; and
- delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of effective mitigation procedures.”

*Risks and benefits of other study interventions and procedures should be evaluated according to the criteria set out in Guideline 4 – Potential individual benefits and risks of research.*\(^{(1)}\)

A WHO expert group has identified five situations when placebos may be acceptable in the context of vaccine trials despite the existence of an effective intervention, namely when the existing vaccine: (1) is not affordable or not accessible to the target population, (2) has not been proven effective in the target population, (3) has been proven ineffective in the target population, (4) has an unknown or uncertain public health impact in the target population which is to be evaluated against a placebo; or (5) is not acceptable to target population (e.g. a vaccine containing porcine gelatine in populations that have religious restrictions on the consumption of pork). However, the risks and benefits of conducting a placebo-controlled design should always be weighed against those of alternative trial designs such as response-adaptive designs, observational studies, or historical comparisons.\(^{(1,2)}\)

The use of placebo may require risk mitigation even if no established effective intervention exists. For example, in the Ebola vaccine trial conducted in Guinea the use of a placebo or an unrelated vaccine in the control group was deemed ethically unacceptable as it would leave vulnerable individuals unprotected against Ebola virus disease when a potentially effective investigational vaccine was available. Instead, vaccination of control subjects was delayed by 21 days, the minimal delay that would enable researchers to determine vaccine efficiency.\(^{(3)}\)

**The use of drug kits**
Specifically for researching new pharmaceuticals, clinical trials should preferably have a randomized double-blind design. Blinding can take place at several levels: it may apply to the researchers who assign subjects to groups, the subjects themselves, the health care workers who take care of patients in a study, and the researchers who record and assess the outcomes.\(^{(4)}\)

A method of blinding clinical trials is the use of drug kits, in which the investigational or control product is packaged for distribution to investigational
sites. Each kit is labelled with a neutral ID, without indication of its content, enabling investigators to administer study or control drug to subjects in a blinded manner without the assistance of an unblinded pharmacist. Each kit contains sufficient product for a extended period, typically two or three weeks, although the quantity will vary depending on the study design.

The key component to the successful use of drug kits is the creation of a kit list, where kit IDs are randomly assigned to kit types (investigational or control). This kit list is used at the time of manufacture to label the kits, during shipping to track the kits, and during the study to assign kits to patients.

Many trials involve multiple clinical sites. To avoid the need for an unblinded pharmacist at each site, use is often made of a randomization centre to randomize study subjects and manage the supply of drug kits, track drug kit inventory at each site, ship kits to sites, and assign kits to patients. In this way, information on whether a kit contains test or control product does not accompany the kit but is available from the randomization centre.

The coding used in creating the kit list and the distribution patterns and resupply methods employed are key factors in blinding a clinical trial. A good design should achieve a balance between kit efficiency and successful blinding. This can be illustrated by two simple scenarios. In a trial where each kit handed out to a subject triggers a replacement by a single kit of the same type, no kits are wasted but the researcher can deduce that the patients dosed with these two kits belong to the same study arm. In the opposite scenario the randomization centre would send two replacement kits (one active and one control) for each kit handed out to a patient, and would inactivate one of the two when a kit is assigned to the next patient. This is successful blinding at the expense of wasting one kit per subject.

An analogous approach to the “waste-one-kit” method could be used to blind a trial where the control subjects receive a delayed intervention, by scheduling additional visits in both groups. In the Ebola vaccine trial conducted in Guinea this was not possible due to operational challenges; instead, to reduce the risk of bias arising from behaviour changes that might follow vaccination, participants were informed that it is not known if the vaccine works, and that they must still take steps to avoid infection.

In practice, the design of algorithms for coding and supplying blinded drug kits will take into account a range of factors specific to each study, such as any additional trial arms, kit inventory size, enrolment rate at the sites, and times between subject enrolments in relation to shipment time for replacement kits. Operational characteristics of different types of kit lists and supply methods have been discussed in published literature. A criterion has also been proposed for evaluating the strength of blinding in a clinical trial, even if the researcher has been unblinded to the contents of one or more kits. This is of interest because it is not uncommon for an investigator to be unblinded to a subject’s treatment assignment for safety reasons or from the subject’s adverse event or efficacy profile.

Conclusions
With today’s swift pace of product development in a globalized market, designing, assessing, and authorizing clinical trials can be challenging. Cooperation among regulators, ethics committees, and sponsors to reach consensus on key ethical
and regulatory questions is essential, and has proved particularly valuable in situations of urgency and in low-resourced environments.(7)

Efficient conduct of the trials without unnecessary regulatory barriers is equally important. Excessively cumbersome regulations, for example on importation and dispensing of placebos for clinical trials, could delay access to effective and sometimes lifesaving medicines. WHO stands ready to assist countries in identifying well-balanced approaches for clinical trials, including those requiring the use of placebos.

Lastly, well-designed clinical trials must be complemented by reliable post-approval safety assessment mechanisms. Many new medicinal products are introduced early and/or exclusively into countries with limited pharmacovigilance capacities. New guidance has become available on safety surveillance of vaccines, proposing a structured process for evaluating whether significant knowledge gaps exist, whether passive safety surveillance is adequate, and if not, how active vaccine safety surveillance studies can be designed and implemented.(8)

References

Quality monitoring

Survey of the quality of selected antiretroviral medicines circulating in five African countries

This article presents an overview of the findings of a sample testing survey organized by WHO as part of its quality monitoring activities for medicines. The survey confirmed the positive impact of WHO prequalification in assuring the quality of antiretrovirals used in HIV treatment programmes of WHO Member States. A full report of the survey is in preparation.

Introduction
A quality survey was organized in 2015 and 2016 by the WHO Prequalification Team (WHO-PQT) in cooperation with the National Medicines Regulatory Authorities/Ministries of Health in five countries in Sub-Saharan Africa. The objective of the survey was to assess the quality of selected antiretroviral medicines (ARVs) obtained at approved (authorized or accredited) public and private sector procurement and treatment sites.

This is the fifth survey of this nature organized by WHO-PQT. Reports of previous surveys are available on the WHO website. (1,2,3,4) The survey results are intended to assist the responsible authorities in participating countries to evaluate their markets and propose possible strategies and implementation plans to address any problems identified. In addition, the active engagement of regulatory staff is expected to help build capacity for coordinated post-market quality surveillance in WHO Member States.

Methodology
Medicines samples were collected at official public and private sector procurement and treatment centres in Burkina Faso, Democratic Republic of the Congo (DRC), Nigeria, Rwanda and Zambia. The survey targeted selected ARVs used in large volumes as reported by international procurers. The focus was on those products with the highest probability of quality problems, prioritizing paediatric formulations – for which there has been a steady increase in prequalification in the past five years – and products of which substandard or falsified versions had been reported to the WHO Global Surveillance System. (5) The following ARVs were included in the survey:

- efavirenz 600mg tablets;
- efavirenz/emtricitabine/tenofovir disoproxil fumarate 600/200/300mg tablets;
- lamivudine 150mg tablets;
- lamivudine/nevirapine/zidovudine 30/50/60mg dispersible tablets;

This article was contributed by Mr Rutendo Kuwana and Dr Jitka Sabartova, who jointly coordinated the quality testing survey.
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Quality monitoring

Survey of the quality of selected ARVs in five African countries

- lamivudine/ nevirapine/ zidovudine 150/200/300mg tablets;
- lamivudine/ zidovudine 30/60mg dispersible tablets;
- lamivudine/ zidovudine 30/60mg tablets;
- lamivudine/ zidovudine 150/300mg tablets; and
- nevirapine 50mg dispersible tablets.

The quality of the samples was verified by testing at four WHO-prequalified laboratories according to the monographs of The International Pharmacopoeia, British Pharmacopoeia and US Pharmacopeia as applicable. Testing according to official pharmacopoeial monographs made it possible to compare products from different manufacturers. However, individual products may be registered in countries or prequalified by WHO with methods and specifications that differ from those set for this survey. The protocol therefore required that if a sample of a prequalified product was found to be out of specification when using the pharmacopoeial method, it was to be re-tested using the manufacturer’s validated method accepted by WHO-PQT. The decision on compliance was then based on the result of the method used in the re-testing.

The survey was conducted in good compliance with the pre-established protocol. As in previous surveys organized by WHO-PQT, the outcomes were discussed with representatives of regulatory authorities, who participated in the formulation of recommendations.

Results

Number of samples tested
A total of 126 samples were collected and tested.

Origin of samples
The samples collected represented medicines produced by eight different manufacturers, all of whom were based in India. The authenticity in terms of batch number, manufacturing and expiry dates, and manufacturing site was confirmed for all samples by the relevant manufacturers. Therefore it is highly unlikely that any falsified products were present among the collected samples.

The large majority of samples (98%, 123 of 126 samples) were of WHO-prequalified products.

Testing results
Of the 126 samples tested, 125 fully complied with the specifications set for the survey. This included two samples that did not comply with pharmacopoeial specifications during initial testing, but complied when re-tested with approved manufacturer’s methods.

There was only one non-compliant finding in the survey: In one of two collected containers of a sample the tablets were stained with drying agent from a burst sachet, causing them to fail the pharmacopoeial requirements for appearance. The stained tablets were excluded from further testing.

Discussion
The survey provided a snapshot picture of the quality of the sampled products and generated information about the availability of the target medicines in selected countries, their prequalification and registration status, and the storage conditions in procurement and treatment centres in participating countries.

Testing at WHO-prequalified laboratories according to the common protocol and specifications can be considered as reliable.
However, when interpreting the outcomes of the survey it should be kept in mind that the results relate to a limited set of countries, a specific selection of medicines and a limited number of samples taken at official procurement and treatment centres.

The survey showed that pharmacopoeial methods are not always applicable for quality control of specific products. Although in the majority of cases they seemed to be sufficient to control products appropriately, there were two cases where – contrary to the approved manufacturers’ methods – they provided marginally failing results.

Compared with the results of the study organized by WHO-PQT in 2007, the failure rate decreased from 1.8% to 0.8%, indicating a marginal improvement of the quality of ARVs found in official distribution and treatment centres. The share of prequalified products among samples increased from 53% to 98%. The survey reconfirmed the positive impact of WHO prequalification in making ARVs of consistently good quality available for procurement in countries.

In the five quality surveys organized to date by WHO-PQT across product categories, 113 of 682 non-prequalified product samples failed to comply with specifications, compared with only seven of 464 WHO-prequalified product samples. For two of the seven it could be shown that the problem was likely caused after manufacture. These results demonstrate that WHO prequalification reliably assures uniform quality standards.

ARVs procured for HIV treatment programmes are mostly donor- or government-funded, and are typically subject to quality policies that require them to be WHO-prequalified or approved for use in a stringent regulatory environment. As can be expected, all the samples collected in the survey were of imported products, none of them represented locally produced medicines.

The complexity of procurement and distribution of ARVs was illustrated by the fact that some manufacturers did not know to which markets their products were supplied in the end, and re-distribution of medicines among countries was frequent. This highlights the importance for regulators to take into account the risks associated with such complex supply channels.

In principle, the selected medicines were available at procurement and treatment centres, although there were differences in the number of generic versions that were available. For certain medicines targeted in the survey the availability was influenced by local therapeutic guidelines and practices.

Rigorous registration policies are applied in some participating countries – notably in Nigeria and Zambia – but other legally acceptable mechanisms that bypass normal registration processes are also used to ensure a continued supply of needed medicines, as was the case in Burkina Faso, DRC and Rwanda. It was not assessed to which extent the responsible national authorities verified whether the ARVs targeted in this survey were in line with the specifications and conditions accepted by WHO-PQT, for example by using the WHO collaborative registration procedure. Four of the five countries included in the survey (Burkina Faso, DRC, Nigeria and Zambia) were participating in the collaborative procedure at the time of the study. However, only two products registered through this pathway were sampled in the survey, namely lamivudine 150mg tablets and lamivudine/zidovudine 150/300mg tablets in Nigeria.

A list of collaboratively registered products is available at https://extranet.who.int/prequal/content/collaborative-registration-faster-registration.
The survey results further indicate that storage conditions in procurement and treatment centres in participating countries were in principle under control and did not have a negative impact on medicines quality.

Conclusions and recommendations
Although antiretrovirals with a higher probability of substandard quality were targeted in this survey, the results indicate that ARVs available at official procurement and treatment sites are of good quality.

The method of multistate collaborative sampling, centralized testing, with common data analysis, has once more proved to be a useful approach in independent quality monitoring of prioritized medicines. The approach was commended by participating countries during the debriefing session.

It was recommended that future surveys should incorporate non-destructive in-country screening before samples are submitted to designated laboratories, and that parallel in-country testing of samples in national quality control laboratories could be conducted as an element of proficiency testing to build capacity and confidence. WHO should also make efforts to develop data-sharing platforms or repositories of testing results for use by Member States.

References
Safety news

Safety warnings

**Dulaglutide:**
**Anaphylaxis and angioedema**
*Japan* – The PMDA has informed health professionals that cases of anaphylaxis have been reported in patients treated with dulaglutide (Trulicity®) outside Japan. Angioedema-related symptoms have been frequently observed in the cases associated with anaphylaxis, and independent cases of angioedema have also been reported. The product information in Japan will be updated to reflect the risk of these adverse events.

► [PMDA Summary of investigation results and MHLW Revision of precautions, 30 May 2017.](#)

**Darbepoetin alfa:**
**Severe skin reactions**
*Canada* – Health Canada has informed health professionals about international reports of severe blistering, mucosal ulceration, and exfoliation cutaneous reactions, including life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis in patients treated with darbepoetin alfa in the post-marketing setting. No cases have been reported in Canada. Darbepoetin alfa is indicated for the treatment of anaemia associated with chronic kidney disease or anaemia in cancer patients receiving chemotherapy.

► [Health Canada Advisory, 5 May 2017.](#)

**Caspofungin:**
**Severe skin reactions**
*Japan* – The MHLW and PMDA have jointly recommended updates to the product information for the antifungal medicine caspofungin acetate to warn about the risk of toxic epidermal necrolysis and Stevens-Johnson syndrome. This follows reports of cases of these serious skin reactions in patients treated with caspofungin acetate both in Japan and elsewhere. Similar updates have been made to the product information in the U.S. and Europe.

► [PMDA Summary of investigation results and MHLW Revision of precautions, 20 April 2017.](#)

**Pneumococcal vaccine:**
**Injection site necrosis**
*Japan* – The PMDA/MHLW have recommended to update the product information for pneumococcal vaccine (Pneumovax®) to advise health professionals that the cellulitis-like reactions that can occur primarily on the injection site may result in necrosis or ulcer. This follows reports of injection site necrosis or ulcer reported in patients immunized with pneumococcal vaccine in Japan.

► [PMDA Summary of investigation results and MHLW Revision of precautions, 30 May 2017.](#)

**Pembrolizumab:**
**Severe skin reactions**
*Canada* – Health Canada has informed health professionals that cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcomes,
have been reported in patients treated with the cancer medicine pembrolizumab (Keytruda®). Patients should be counselled about this risk and early symptoms. In case of a severe skin reaction pembrolizumab should be suspended and patients referred for immediate specialized evaluation and treatment. Pembrolizumab should be permanently discontinued if SJS or TEN is confirmed. The product information is being updated to include these recommendations.


**Myocarditis**

Japan – Following reported cases of myocarditis in patients treated with pembrolizumab, the MHLW and PMDA have recommended updates to the product information to reflect the risk of this adverse event.

► PMDA Summary of investigation results and MHLW Revision of precautions, 20 April 2017.

**Vemurafenib:**

Fibrosis in hands and feet

New Zealand – The marketing authorization holder, in consultation with Medsafe, has informed health professionals of the increased risk of Dupuytren's contracture and plantar fascial fibromatosis in patients treated for melanoma with vemurafenib (Zelboraf®). These conditions are characterized by thickening or appearance of visible cords in the hands and feet. The product information has been updated to recommend temporary or permanent discontinuation of vemurafenib in case of these adverse events, and to provide guidance on dosage modification.

► Medsafe Safety information, posted 27 March 2017.

**Denosumab:**

Fractures after discontinuation

Japan – The MHLW and PMDA have informed health professionals that multiple vertebral fractures, which may be associated with a temporary increase in bone resorption, may occur in patients with osteoporosis after discontinuation of denosumab, and that transitioning to an alternative antiresorptive agent should be considered when denosumab is stopped.

A higher incidence of multiple new vertebral fractures was seen in patients that had discontinued denosumab compared with placebo in follow-up clinical studies. The time to onset was not inconsistent with that of a temporary increase in bone resorption observed after stopping denosumab in pre-approval clinical studies. The product information for denosumab is being updated to reflect this information.

► PMDA Summary of investigation results and MHLW Revision of precautions, 20 April 2017.

**Gadolinium contrast agents:**

Accumulation in the brain

European Union – The EMA’s Pharmacovigilance and Risk Assessment Committee (PRAC) has concluded its review of gadolinium agents used to enhance magnetic resonance imaging (MRI) body scans. The PRAC has recommended suspension of marketing authorizations for four linear gadolinium contrast agents, *i.e.* intravenous injections of gadobenic acid, gadodiamide, gadopentetic acid and gadoversetamide. Instead, macrocyclic agents should be used at the lowest dose that enhances images sufficiently to make diagnoses, and only when unenhanced body scans are not suitable.

The review found convincing evidence of gadolinium accumulation in the brain.
Although this has not been linked to any symptoms or diseases the PRAC took a precautionary approach, noting that data on the long-term effects of gadolinium in the brain are limited.

Two linear agents will remain available: gadoxetic acid used at a low dose for liver scans, which meets an important diagnostic need, and a formulation of gadopentetic acid injected directly into joints, which has a very low gadolinium concentration. Both agents should be used at the lowest dose that enhances images sufficiently to make diagnoses and only if unenhanced scans are not suitable.\(^{(1)}\)

At the request of some marketing authorization holders of gadolinium-containing contrast agents a re-examination will be conducted and is expected to conclude in July 2017.\(^{(2)}\)

**United States of America** – The FDA has announced that to date it has not identified any harmful effects with brain retention of gadolinium-based contrast agents for MRIs, and that its review will continue. The Agency plans to hold a public meeting in the future to discuss this issue.\(^{(3)}\)

\(^{(1)}\) EMA Press release, 10 March 2017.  
\(^{(2)}\) EMA News, 5 May 2017.  

**Restrictions**

**Codeine, tramadol:** Further restrictions

**United States of America** – The FDA has further restricted the use of codeine- and tramadol-containing medicines in children due to the serious risk of slowed or difficult breathing which can be potentially fatal. Codeine is contraindicated to treat pain or cough in children under 12 years of age, and tramadol is contraindicated to treat pain in these children. Neither medicine should be used in adolescents aged 12–18 years who are obese or have conditions such as obstructive sleep apnoea or severe lung disease.

Single-ingredient codeine-containing products and all tramadol-containing products are FDA-approved only for use in adults. The FDA has also recommended against the use of codeine and tramadol medicines in breastfeeding mothers due to the risk of adverse reactions, including serious, potentially fatal breathing problems.

\[^{ }(\text{FDA Drug safety communication, 20 April 2017.})\]  
\[^{ }(\text{FDA Statement, 20 April 2017.})\]

**Australia** – The TGA has informed health professionals that following a December 2016 decision, all medicines containing codeine will be rescheduled as prescription medicines with effect from 1 February 2018, and may then no longer be advertised to the public.

\[^{ }(\text{TGA. Changes to advertising for medicines containing codeine. 8 May 2017.})\]

**To be removed from the market**

**Oxymorphone injection:** Abuse, dangerous consequences

**United States of America** – The FDA has requested the removal of oxymorphone hydrochloride injection (Opana ER\(^*\)) from the market. A review of all available post-marketing data had shown a significant shift in the route of abuse from nasal to injection, following the product’s reformulation as an injection. The injection abuse of the product has been associated with a serious outbreak of HIV and hepatitis C, as well as cases of thrombotic microangiopathy, a serious blood disorder.
This is the first time that a currently marketed opioid pain medication is removed from sale in the U.S. due to the public health consequences of abuse. The product had been reformulated 2012 to reduce the potential for abuse; however, the reformulation has had unintended consequences. As a part of the its response to the opioid epidemic in the United States, the FDA will continue to examine the risk-benefit profile of all approved opioid analgesic products and will take further actions as appropriate.
► FDA News release, 8 June 2017.

**New prescribing guidelines**

**Vancomycin:**
*Fighting antimicrobial resistance*

*European Union* – The European Medicines Agency (EMA) has recommended changes to the prescribing information for vancomycin to ensure its appropriate use in the context of the fight against antimicrobial resistance. Vancomycin remains an important therapeutic option for the treatment of serious infections. The updated recommendations are as follows.

- Vancomycin infusion can continue to be used for the treatment of serious infections caused by certain bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and to prevent bacterial endocarditis in patients undergoing surgery. The starting dose should be calculated according to the age and weight of the patient. Any dose adjustments should be based on serum concentrations to achieve the target therapeutic concentrations.
- Oral vancomycin should be used only to treat *Clostridium difficile* infections. The maximum dose should not exceed 2 g per day. In patients with inflammatory intestinal disorders, vancomycin serum concentration should be closely monitored. Children under 12 should be given age-appropriate formulations. Oral vancomycin should no longer be used to treat staphylococcal enterocolitis or for gastro-intestinal decontamination in immunocompromised patients.
- Vancomycin formulations authorized for intraperitoneal use can continue to be used to treat infections in patients undergoing a peritoneal dialysis.


**Opioids:**
*Updated prescribing guidance in Canada*

*Canada* – The Government of Canada has announced the publication of an updated guideline on opioid prescribing to mitigate the impact of the current opioid crisis. The guideline recommends that patients with chronic non-cancer pain should first try non-opioid options to manage pain before considering a trial of opioid therapy. Patients starting opioid therapy should be given less than 90 morphine equivalents daily (MED) and the maximum prescribed dose should be restricted to less than 50 mg MED. Patients already on high doses of prescribed opioids (90 mg MED or more) should be encouraged to taper the doses gradually in collaboration with their prescribers, with multidisciplinary support offered to those who experience challenges.

Health Canada and the Canadian Institutes of Health Research provided funding for the updating of the guideline and associated training tools for prescribers, as part of efforts to address problematic prescription drug use.
**Known risks**

**Eluxadoline:**

**Risk of pancreatitis in certain patients**

**United States of America** – The FDA has warned that eluxadoline (Viberzi®), used for the treatment of irritable bowel syndrome with diarrhoea, should not be given to patients who do not have a gallbladder. An FDA review found that these patients have an increased risk of developing serious pancreatitis that could result in hospitalization or death. Pancreatitis may be caused by spasm of the sphincter of Oddi in the small intestine.\(^{(1)}\)

In the EU, a similar warning was included in the product information for eluxadoline (Truberzi®) in 2016 at the time of approval.


**Canagliflozin:**

**Lower limb amputations**

**United States of America** – The FDA has confirmed the increased risk of leg and foot amputations with the diabetes medicine canagliflozin, and has required new warnings, including the most prominent “Boxed Warning” to be added to the product information for canagliflozin to describe this risk. This follows an FDA warning published in May 2016 on the basis of interim clinical trial results.\(^{(1)}\)

Earlier in 2017 the EMA had confirmed this risk for canagliflozin and had required updates to the product information. A warning about this potential risk was also added to the product information of dapagliflozin and empagliflozin.\(^{(2)}\)

► \(^{(1)}\) [FDA Drug Safety communication, 16 May 2017.](https://www.fda.gov/Drugs/DrugSafety/ucm564157.htm)


**Certain hepatitis C medicines:**

**Interaction with ethinyloestradiol**

**Australia** – The TGA has advised health professionals that, while in the product information for the hepatitis C medicines Viekira PAK* (paritaprevir/ritonavir/ombitasvir tablets and dasabuvir tablets) and Viekira PAK-RBV* (paritaprevir/ritonavir/ombitasvir tablets, dasabuvir tablets and ribavirin tablets) the use of ethinyloestradiol-containing medicines is listed as a contraindication, not all ethinyloestradiol-containing medicines currently provide similar information.

In clinical trials for the hepatitis C medicines, elevations of liver enzymes to more than five times the upper limit of normal occurred in approximately 1% of participants, and occurred more frequently in women taking contraceptives containing ethinyloestradiol. Contraceptives containing ethinyloestradiol must be discontinued prior to starting treatment and alternative contraceptive agents used. Ethinylestradiol-containing medicines can be restarted approximately two weeks following completion of treatment with Viekira PAK* or Viekira PAK-RBV*.


**Bosutinib:**

**Severe skin reactions**

**Japan** – A warning about the risk of toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme has been added to the product information of bosutinib, used to treat certain forms of leukaemia. This follows reported cases of these severe skin reactions in patients treated with bosutinib in Japan.

This risk is also reflected in the product information for bosutinib approved in the EU.

**Ponatinib:**
**Update on dose adjustment**
United Kingdom – The MHRA has provided health professionals with an update on dose modifications to mitigate the risk of blood vessel blockages with ponatinib (Iclusig®). For patients with chronic-phase chronic myeloid leukaemia who have achieved a major cytogenetic response while on treatment, the dose can be reduced to 15 mg/day based on an individual patient assessment. If the dose is reduced, close monitoring of response is recommended.

This advice is supported by additional long-term follow-up data that have become available since this risk was first communicated in 2014.

► MHRA Drug Safety Update volume 10, issue 9, April 2017: 2.

**Idelalisib:**
**Risk of serious infections**
Canada – Health Canada has updated the product information for the cancer medicine idelalisib (Zydelig®) to warn about the increased risk of serious and potentially fatal infections, and to recommend antibiotic prophylaxis against *Pneumocystis jirovecii* pneumonia and monitoring of patients for cytomegalovirus infection. Idelalisib is not authorized in Canada for use in first-line chronic lymphocytic leukaemia and early-line indolent non-Hodgkin lymphoma outside of a clinical trial.

In 2016 a number of clinical trials involving idelalisib had been stopped due to serious side effects, and several regulatory authorities initiated safety reviews and published safety communications. In the EU, product information was updated in July 2016 with recommendations to mitigate this risk.


**Hypnotics and anxiolytics:**
**Risk of dependence even with recommended use**
Japan – The PMDA has completed its review of dependence-related adverse events reported with the use of hypnotics and anxiolytics. The review had been requested by the Ministry of Health, Labour and Welfare (MHLW) in view of the high reported use of hypnotics and anxiolytics in Japan. The PMDA recommended updates to the product information for these medicines to emphasize the risk of dependence regardless of patients’ predispositions to drug abuse and to warn against prolonged use even for approved indications and at recommended doses.

To discourage inappropriate prescribing, a demerit point system had been introduced in Japan as part of the 2012 and 2014 revisions to health insurance regulations. Furthermore, given that risk of abuse was confirmed for zopiclone and etizolam, the MHLW had issued an announcement in September 2016, newly specifying these drugs as psychotropics and recommending a maximum treatment duration of 30 days.


**Anaesthetics and sedatives in young children:**
**Harm to developing brain**
United States of America – The FDA has approved previously announced changes to the product information of general anaesthetic and sedation medicines, warning against their lengthy or repeated use in children under 3 years of age and in pregnant women during the third trimester. Data from studies in young animals suggest that exposure to these medicines for more
than 3 hours can cause widespread loss of nerve cells in the developing brain.
▶ FDA Drug safety communication, 27 April 2017.

Iodinated contrast media: Hypothyroidism, affecting growth and development
Canada – A Health Canada assessment has revealed a possible association between exposure to iodinated contrast media (ICM) and development of hypothyroidism in adults and children, particularly in infants. Hypothyroidism in infants may be harmful for growth and development, including mental development. The Agency encourages healthcare professionals to evaluate and monitor thyroid function in infants exposed to ICM, and if abnormal, continue to monitor until it has normalized. Prescribing information for these products will be harmonized to include this information.

In 2015 the FDA had requested manufacturers to include information related to rare cases of hypothyroidism reported in infants following the use of ICM products.

Unchanged recommendations

Selexipag: No increased risk of mortality
European Union – The European Medicines Agency (EMA) has completed its review of selexipag (Uptravi®) which was initiated following five patient deaths in France. The data reviewed did not suggest that selexipag is associated with a higher risk of mortality than other medicines used to treat pulmonary arterial hypertension. EMA has confirmed that selexipag can continue to be used by both new and existing patients according to the current prescribing information.

Factor VIII-containing medicines: No differences in inhibitor development
European Union – The EMA has completed its review of factor VIII medicines to evaluate the risk of inhibitors developing in patients with haemophilia A who have not previously been treated with these medicines. The review was triggered by the outcomes of a study which found this risk to be greater with recombinant factor VIII medicines than with plasma-derived ones. The review did not find any clear and consistent evidence of a difference in inhibitor development between the two classes of factor VIII medicines.(1)

A marketing authorization holder has requested a re-examination, which will start upon receipt of the grounds for the request.(2)
(2) EMA News, 9 June 2017.

Mefloquine: Clarifications on adverse events
Canada – A Health Canada safety review launched at the end of 2016 has not found conclusive evidence that mefloquine can cause long-lasting and permanent neurological and psychiatric adverse events. Mefloquine remains a first-line option a first-line option to protect Canadians from malaria when travelling to areas with a high infection risk. The product information for mefloquine will be updated with a checklist of contraindications for prescribers, as well as clearer information for patients on the risk of damage to the vestibular system in
the inner ear, that may, very rarely, become permanent in some patients.
► Health Canada Statement, 1 June 2017.

**Docetaxel:**
No increased incidence of neutropenic enterocolitis

European Union – An EMA review has found that there is no evidence of change in the known risk of neutropenic enterocolitis after treatment with the cancer medicine docetaxel.

The review was triggered by a rise in reported cases in France. The Committee concluded that this rise could be due to increased awareness among healthcare professionals. Reporting rates in the EU as a whole do not provide any evidence of an increase in the incidence of this known adverse effect, which may occur in up to 1 in 1,000 cancer patients taking the medicine.
► EMA Press release, 9 June 2017.

### Reviews started

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<td><strong>Daclizumab</strong> (Zinbryta ®)</td>
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<td><strong>Fingolimod</strong> (Gilenya®)</td>
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<td>Risk of malformations and developmental problems in babies who are exposed to valproate in the womb. This is a follow-up review to determine whether further restrictions are required.</td>
<td>EMA, Article-31 referral: Valproate and related substances, 10 March 2017.</td>
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Non-compliance with good practices

Micro Therapeutic Research Labs: EMA suspends products due to unreliable bioequivalence data

European Union – The EMA has recommended suspending a number nationally approved medicines for which bioequivalence studies were conducted by Micro Therapeutic Research Labs in India. For critically important medicines the national authorities can postpone the suspension in the interest of patients. The Agency also recommended that medicines under evaluation and studied at these sites should not be authorized until bioequivalence is demonstrated using alternative data. For some of the products affected, alternative bioequivalence data were subsequently provided and the suspensions were lifted.

Inspections conducted at the two sites in February 2016 had identified concerns regarding misrepresentation of study data and deficiencies in documentation and data handling. This triggered an EMA review, which concluded that data from studies conducted at the two sites between June 2012 and June 2016 are unreliable. The issue affects more than 300 approvals and applications.


Mylan Laboratories

United States of America – The FDA has warned the India-based company Mylan over issues with quality management and data integrity at its manufacturing site at F4 & F12 Malegaon MIDC, Sinnar, Nashik observed during an FDA inspection in September 2016. (1) According to the Global Fund's Price and Quality Reporting (PQR) database, almost half of all grant-funded antiretrovirals supplied in 2016 were produced by Mylan. (2) WHO has prequalified 21 finished pharmaceutical products manufactured at the Nashik site. Of these, 10 are also manufactured at other Mylan sites which are not affected by the current warning letter. The Prequalification Team had inspected the Nashik site in 2015 and found it compliant after implementation of corrective and preventive action. WHO has recommended increased vigilance and post-shipment testing. The manufacturer has been asked to provide an impact assessment on prequalified products. Thereafter another WHO inspection will be conducted. (3) In an update, WHO-PQT summarized the findings from the impact assessment and concluded that there were no concerns regarding the quality of the WHO-prequalified products manufactured at the Nashik site. (4)

► (1) FDA Warning letter 320-17-32, 3 April 2017.

Qinhuangdao Zizhu

Geneva – The WHO Prequalification Team (PQT) has responded to an FDA import alert issued in March 2017 for products containing APIs from Qinhuangdao Zizhu Pharmaceutical Co Ltd following inspection findings of non-compliance with GMP, including a breach of data integrity in the quality control laboratory. WHO-PQT had inspected the site in 2015 and found it compliant with GMP after completion of corrective action. WHO-PQT is planning to re-inspect the site. Meanwhile it has advised
finished products manufacturers to take additional measures to ascertain the quality of APIs from Qinhuangdao Zizhu, and is working with them to identify alternative API sources.


FDA warning letters
United States of America – A series of warning letters were issued to pharmaceutical companies by the FDA’s Center for Drug Evaluation and Research in March, April and May 2017.\(^{(1)}\)

An FDA inspection of the India-based active pharmaceutical ingredient (API) manufacturer Badrivishal Chemicals & Pharmaceuticals revealed that original records, water testing reports and sample notebooks had been discarded in trash bags, which later disappeared. Impurity testing chromatograms showed repeated unexplained discrepancies in run times, aborted runs and reprocessing of data.

The China-based API manufacturer Lumis Global Pharmaceuticals Co. Ltd. had generated certificates of analysis (COA) by copying and pasting analytical results from the API manufacturers onto its own letterhead. The India-based manufacturer USV Pvt Ltd was warned over repeated violations at multiple sites related to data integrity, validation of aseptic and sterilization processes and other issues. Divi’s Laboratories Ltd in Visakhapatnam, India was warned over their failure to prevent unauthorized access to data as well as manipulation and omission of data. Warnings were also issued to Opto-Pharm Pte Ltd in Singapore, Indoco Remedies Limited in India, Teva’s API manufacturing site in Hangzhou, China, Sal Pharma and Vikshara Trading & Investments Ltd in India, and Changzhou Jintan Qianyao Pharmaceutical Raw Materials in China.

These reports highlight once more the need for stringent regulation and enforcement of adherence to regulatory requirements.

FDA warning letters are available at: www.fda.gov/ICECI/EnforcementActions/WarningLetters/

TGA reminder on good data management requirements
Australia – The TGA has published a statement regarding its expectations regarding data management and integrity. The Agency is reminding applicants that it views data management and integrity issues very seriously, as reflected in its definition of a “critical” deficiency in GMP, which states: “A deficiency in a practice or process that has produced, or may result in, a significant risk of producing a product that is harmful to the user. Also occurs when it is observed that the manufacturer has engaged in fraud, misrepresentation or falsification of products or data.”

The statement goes on to outline the ALCOA+ principles\(^{1}\) – the basis of good data management and integrity practices – as described in the draft guidelines of the Pharmaceutical Inspection Co-operation Scheme (PIC/s). The TGA intends to use these guidelines as reference in its regulatory inspections and dossier review.

TGA Statement, 6 April 2017.


\(^{1}\) ALCOA+: Attributable, Legible, Contemporaneous, Original, Accurate; + complete, consistent, enduring, available.
Falsified product alerts

Meningococcal ACWY vaccine in West Africa
The following is reproduced text from the WHO Medical Product Alert No. 1/2017 relating to the circulation of a confirmed falsified meningococcal ACWY vaccine discovered in Niger.

Product details
This product is used to immunize against Meningococcal disease serogroups A, C, W, and Y. Meningococcal meningitis vaccine is listed as a WHO Essential Medicine.
On 31 May 2017, the manufacturer “Bio-Manguinhos/Fiocruz” informed WHO that a falsified version of the following product was available in Niger.

Product name: Polysaccharide Meningococcal ACWY Vaccine
Batch number: 089UMH002 Z
Expiry date: 092017
Date of manufacture: 092014

The label on the product claims that it is manufactured by Bio-Manguinhos/Fiocruz and is presented in vials of 10 doses each. The falsified product had not yet been subject to laboratory analysis at the time of publishing the Medical Product Alert.
The manufacturer Bio-Manguinhos/Fiocruz has stated that:

- They do not manufacture Polysaccharide Meningococcal ACWY Vaccine.
- Based on examination of the photographs they can confirm that this packaging is falsified.

No adverse events following immunisation attributed to this falsified vaccine are known to have been reported at this stage. On the basis of the above information, any Meningococcal ACWY Vaccine claiming to be manufactured by “Bio-Manguinhos/Fiocruz”, should be considered falsified and reported.

Advice to health care professionals, patients and national authorities is provided in the WHO medical product alert. Authorities are asked to immediately notify WHO if these falsified products are discovered in their country by contacting rapidalert@who.int

► WHO Medical Product Alert No. 1/2017, 2 June 2017 (includes photographs).

Hepatitis C medicine in Germany
The German regulatory authority has informed health professionals and the public that the following falsified product has been discovered in a pharmacy in the state of North Rhine-Westfalia.

Product: Harvoni® 90 mg / 400 mg tablets
Batch number: 16SFC021D (this lot number exists for the genuine product on the German market)
Expiry date: 06/2018
Colour: The tablets are white instead of orange.

The content of the falsified tablets is not yet known; laboratory analysis is ongoing. The manufacturer of the genuine product, Gilead, has organized a recall of the lot with the above-mentioned number from the German market.

► Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM). Press release 9/17, 6 June 2017 (in German).
Pre-market assessment

Assessment of generics in China: Demonstrating interchangeability
In 2016 the State Council of the Government of China launched a policy requiring that all oral solid preparations of generic medicines on the National Essential Drugs List (2012) approved before 1st October 2007 should be evaluated by the end of 2018, with a possibility to extend the deadline until the end of 2021 in case of special circumstances, for example if clinical trials are required.\(^{(1)}\)

More details about this policy are found in a recently published commentary, the abstract of which is reproduced below.\(^{(2)}\)

Generic drugs should be interchangeable with originators in terms of quality and efficacy. With relative lower prices, generic drugs are playing an important role in controlling health expenditures and ensuring access. However, the widespread understanding of “cheap price equals low quality” has a negative impact on the acceptance of generic drugs. In China, medical doctors doubt the efficacy and quality of generic drugs manufactured domestically. To address these concerns, the Chinese State Council released a policy in 2016 to ensure the interchangeability by re-evaluating the quality and efficacy of generic drugs. It intends to make up a missed lesson in the regulation to be in line with internationally accepted practices. Generic drugs firms, depending on the availability of appropriate comparators, should conduct either comparative bioequivalence studies or full scale clinical trials. The re-evaluation will be implemented in a stepwise approach with the essential medicines covered in the first step. The policy could achieve several benefits by increasing confidence on the Chinese produced generic drugs, upgrading regulatory standards, streamlining the Chinese generic drug industry and creating a healthy competition market. Nevertheless, enormous challenges remain in enlarging the capacity to review applications, selecting appropriate comparators, ensuring the capacity of domestic clinical research sites, and achieving the acceptance of re-evaluated generic drugs.


New fast-track pathway in India: WHO-recommended combinations
India – The Drugs Controller General of India has issued a notice outlining a fast-track regulatory approval pathway for combination products recommended in WHO guidelines and which are used to treat HIV infection and subtypes of hepatitis B and C relevant to the Indian population. The fast-track provisions apply regardless of whether the specific combination product has been previously approved elsewhere.

The fast-track provisions apply regardless of whether the specific combination product has been previously approved elsewhere. The new pathway includes provisions for waiving clinical trial requirements and for early submission of abbreviated data with a commitment that complete data will be submitted prior to approval. The rationale is that combinations recommended in WHO treatment guidelines are considered to have...
a positive risk-benefit balance, and that they are falling under the category of “extreme urgency” as defined in national regulations. ► CDSCO Notice, 20 March 2017.

Australian orphan drug programme: Reforms and transition arrangements

Australia – The TGA has announced updates to its orphan drug programme to align it with the practices of other regulatory authorities and to target the most important unmet needs. The changes take into account feedback received in two public consultations. The threshold and eligibility criteria will be adjusted so that more conditions may qualify as orphan diseases, and the validity period of orphan drug designation will be limited to 6 months, with a possibility of extension to 12 months with written justification. The changes are effective from 1 July 2017. Transition arrangements are in place for existing designations made at a time when their status would not lapse.

(1) TGA. Submissions received and TGA response: Orphan drug program. 18 April 2017.
(2) TGA. Reform of the Orphan Drug Program - Transition arrangements.

EU Priority medicines scheme: One year on

European Union – The EMA has met with stakeholders to look back on one year’s experience with its PRIME (PRIority MEdicines) scheme. Of 96 requests processed, 20 were approved including 8 for orphan medicines. Among the requests that were not granted, approximately 70% lacked sufficiently robust data, about 40% had an insufficient justification of therapeutic advantage, and about 20% were at an advanced stage of development process was already so that the use of the scheme would not have been effective.

The PRIME scheme was launched in March 2016 to provide early support to developers of medicines targeting unmet treatment needs. It assists applicants in optimizing development plans, collecting robust data and submitting high quality applications enabling timely authorization of needed products.


EU medical devices regulation: Strengthened rules

European Union – The European Parliament has adopted two new regulations on medical and in vitro diagnostic medical devices. The new rules will impose tighter controls on high-risk devices such as implants, on clinical trials and on the independent notified bodies that can approve the marketing of medical devices. The new rules will also cover certain previously unregulated aesthetic products. A new system for risk classification in line with international guidelines will apply to in vitro diagnostic medical devices (IVDs). The rules will also improve the traceability of medical devices in the supply chain by using a unique identification number reflected in the new European database of medical devices (EUDAMED). Manufacturers will be obliged to collect data about their performance and EU countries will coordinate more closely in the field of market surveillance.

Medical devices such as diagnostics, companion tests and delivery devices are playing an increasingly important role in guiding and supporting the use of medicines. The new rules address the need for revision of the existing regulatory framework and for stronger market surveillance in the area of medical devices.
The rules were adopted by the European Parliament in April 2017, for publication in the Official Journal in May. They will become effective after a transitional period of three years from publication for medical devices and five years from publication for in vitro diagnostics.


**Adverse events reporting**

**Pharmacovigilance in Europe: Updates and system upgrade**

European Union – The following revised guidance has been published on the Agency’s Good Pharmacovigilance Practice (GVP) website: *Module II – Pharmacovigilance system master file (Rev 2)*, which completes the transition to the 2010 EU pharmacovigilance legislation including the “Article 57” database for medicinal products, and a major revision of *Module V – Risk management systems* along with consequent revisions of *Module XVI – Risk minimisation measures*. The GVP introductory cover note has been updated accordingly. (1)

In addition, the EMA’s experience with its coordinated “single assessments” of manufacturers’ periodic safety update reports (PSUR) is reflected in two new documents: an explanatory note on the GVP Module VII addressing issues that have been raised by companies, and a question-and-answer document that guides assessors throughout the evaluation process. In the single assessment process the EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) reviews all PSURs for medicines containing the same active substance(s) together. Each review is led by an assessor from one nominated national authority. The recommendations are legally binding in all EU Member States. Before the introduction of this process in 2015, marketing authorization holders submitted their PSURs for nationally authorized medicines separately to each national authority. (2)

In May 2017 a new and improved version of EudraVigilance successfully passed an independent audit leading to a positive recommendation by the PRAC. EudraVigilance is the European information system of suspected adverse reactions to medicines. The enhanced system will be launched in November 2017. (3)

► (1) EMA. Good pharmacovigilance practices [website].

(2) EMA News, 6 April 2017.

(3) EMA News, 22 May 2017.

**Adverse events of illicit drugs in UK: New reporting scheme**

European Union – The MHRA has launched a pilot scheme for reporting adverse events observed in people using illicit drugs, particularly new psychoactive substances. The scheme’s reporting form is intended to be used by health professionals working in services such as emergency departments, general practice, drug treatment services, sexual health services and mental health services.

The pilot scheme was created following a marked increase in hospital admissions for poisoning by psychostimulants with abuse potential. The data from the pilot are intended to support provision of clinical guidance to professionals.

Supply

GMP for compounded medicines
Australia – The TGA has published new guidance text to assist companies and pharmacists in the interpretation of the PIC/S good manufacturing practice (GMP) requirements for compounded medicinal products. The text provides point-by-point annotations to the main chapters of the PIC/S GMP guide as well as its annexes on manufacturing sterile products and on computerized systems.

Compounding is the preparation of a medicine under the supervision of a pharmacist to meet the specific needs of a patient when no suitable authorized dosage form is available. The guidance provides valuable detail on how to implement good practices in compounding to ensure patient safety.


Reporting of shortages in Canada: Now mandatory via new website
Canada – Pharmaceutical companies are now required by law to report medicines shortages and discontinuances on a new, independent website1. The following must be reported: an anticipated drug shortage; a discontinuation of a drug six months in advance; and any previously unreported shortage within five days of learning about it.

The new website replaces the industry-run website2 where manufacturers have been voluntarily reporting medicines shortages and discontinuances since 2012. The new system offers enhanced notification features and a mobile application. It also provides updated information for health care providers and patients, including tools and guidance to help manage shortages.


Dispensing categories in Switzerland: Revision to encourage self-medication
Switzerland – Changes have been made in Swiss regulations to encourage self-medication without jeopardizing patient safety. Dispensing category C (in-pharmacy sales only) will be abolished. Drugstores will be able to dispense all medicinal products that do not require a prescription (category D), and certain products currently in that category will be reassigned to category E (sale in all shops). Swissmedic is re-evaluating the products concerned, with a focus on the risks of abuse and possible interactions. The Agency is also re-defining the lists of products that can be dispensed by various types of professional therapists. The project is expected to be concluded by 2019.

► Swissmedic Announcement, 10 April 2017.

Antimicrobial resistance

India national action plan
India – The Union Minister of Health and Family Welfare of India has announced the finalization of India’s comprehensive and multi-sectoral National Action Plan to combat antimicrobial resistance (AMR). The announcement was made at the Inter-Ministerial Consultation on AMR containment, where representatives of various Ministries under the Government of India signed a declaration, pledging to strategize collectively to prevent and contain AMR.


New investments in Canada
Canada – Health Canada has announced new rules for veterinary drugs to combat antimicrobial resistance. The new rules impose stricter quality requirements for active pharmaceutical ingredients and restrict the personal importation of certain products. They also require manufacturers, importers and compounders to report annual sales of medically important antimicrobials, and they simplify the importation of low-risk veterinary health products, including those that may be used as alternatives to antimicrobials.(1)

Furthermore, the Government of Canada has announced funding of 1.39 million Canadian Dollars (approximately 1 million USD) from the Canadian Institutes of Health Research to support five research teams whose work will advance innovations in point-of-care diagnostics, with the goal of implementing the best diagnostic tools in healthcare settings and appropriate use of antibiotics.


Tripartite alignment on requirements for antibacterials
European Union, Japan, United States of America – The EMA, the PMDA and the FDA have agreed to align their data requirements for certain aspects of the clinical development of new antibiotics. The Agencies will update their respective guidance documents, and will provide advice to individual medicine developers.

The agreement was reached at the second tripartite meeting to discuss regulatory approaches for the evaluation of antibacterial agents, held in Vienna on 26–27 April 2017. A first tripartite meeting on the subject had taken place in September 2016; a third is planned for October 2017. The alignment aims to stimulate the development of new treatments to fight antimicrobial resistance and protect global public health.

► EMA News, 12 June 2017.

EMA. Second tripartite meeting held between EMA, PMDA and FDA to discuss regulatory approaches for the evaluation of antibacterial agents (webpage).

Collaboration
EU and African regulators meet
Malta – A workshop jointly organized by the EMA and the Maltese Presidency of the EU on 2–3 March 2017 has brought together scientific experts from EMA’s Committee for Medicinal Products for Human Use (CHMP) and regulators from across Africa. The participants discussed how to promote reliance on the scientific output of the CHMP, in particular the Agency’s “Article 58” procedure for global health products intended for use outside the EU. This procedure aims to increase access to high quality, safe and effective medicines by patients in low- and middle-income countries.

This was the first time that CHMP experts met with non-EU regulators in such a forum. The workshop was organized with support from the Bill & Melinda Gates Foundation and WHO. It is in line with the World Health Assembly Resolution WHA67.20, which calls for regulatory systems strengthening.(1)

London – On 18–19 May 2017 a delegation from the East African Community (EAC) visited the EMA to gather information and experience to support the potential
creation of a networking medicines agency for the EAC. The EAC has six partner States: Burundi, Kenya, Rwanda, South Sudan, Tanzania and Uganda. Participants discussed the structure and operations of EMA that could serve as a model for regional collaboration in the regulatory assessment of medicines. (2)

► (1) EMA News, 10 March 2017.
(2) EMA News, 23 May 2017.

Report on EMA–FDA assessment pilot

European Union – The EMA and the US FDA have released the report on their joint pilot programme for the parallel assessment of applications containing Quality by Design (QbD) elements as reflected in ICH Q8, Q9 and Q10 guidelines. The pilot demonstrated a solid alignment between the two Agencies on the implementation of QbD-related concepts, and has opened up a platform for continuous dialogue.

Launched in 2011 and subsequently extended, the pilot programme concluded in April 2016. Two applications for marketing authorization, three variation applications and nine scientific advice applications were evaluated under this programme. The pilot led to the adoption of three sets of Question-and-Answer documents that also addressed comments from the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, which participated as an observer.

► Report from the EMA-FDA QbD pilot program. 19 April 2017.

Swiss–Austrian agreement

Vienna – A memorandum of understanding (MoU) has been signed by the Swiss Agency for Therapeutic Products (Swissmedic) and the Austrian Agency for Health and Food Safety (AGES). The MoU provides a formal basis for intensifying collaboration and for working together on bilateral initiatives. Swissmedic now has cooperation agreements with the medicines regulatory authorities in all German-speaking countries.

(2) AGES Press release, 15 March 2017 (German).

MedDRA expands global reach

Montreal, Canada – Over 5 000 organizations in 103 countries now subscribe to MedDRA, the Medical Dictionary for Regulatory Activities. This reflects the successful adoption of MedDRA as a worldwide standard in the protection of public health.

MedDRA was developed by ICH in the 1990s to facilitate sharing of regulatory information internationally. The update was presented at the MedDRA Management Board meeting, held in Montreal, Canada on 27–28 May 2017. The Board noted the successful collaboration between the MedDRA Maintenance and Support Services Organization (MSSO) and the WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre) in expanding the MedDRA user base, and acknowledged the significant work of the CIOMS SMQ Implementation Working Group in developing Standardised MedDRA Queries (SMQs).

► ICH. Press release, 12 June 2017.

EMA and academia

European Union – The EMA has developed a framework and action plan to formalize and further develop its interactions with the academic community. The aim is to increase academia’s engagement in the
European regulatory system in order to foster technological advances and to ensure that the best scientific expertise is available on time to support regulatory processes and decision-making.

A new webpage has also been published with information on EMA’s activities that are most relevant to academia.
EMA. Academia [webpage].

## Transparency and databases

### Publication of clinical study reports: Release of EMA documents halted

**Luxembourg** – The EU Court of Justice of the European Union has dismissed two appeals by the EMA against interim orders of the General Court, thus upholding the suspension of the release of clinical study reports on two medicines.

This follows court cases brought against EMA in December 2015 by the two pharmaceutical companies manufacturing the respective products. Both companies argue that the release of the documents would infringe their right to protect commercially confidential information contained in their marketing authorization applications. The two cases are still ongoing. Meanwhile the EMA will respect the interim orders and will not release the documents concerned. The Agency will continue to process requests for access to other documents made under the terms of the EU’s Transparency Regulation.

The EMA’s policy on access to documents, which entered into force in 2010, is the EU’s central instrument to achieve transparency in regulatory decision-making. In October 2016, EMA launched its policy on the proactive publication of clinical study reports that support applications for marketing authorization for medicines.

### India builds centralized regulatory portal

**India** – The Drug Controller of India has requested pharmaceutical manufacturers to register their sites on the online “SUGAM” portal. Companies are required to register only once and can then enter information on all their facilities, even if they are located in different States.

The portal was launched in November 2015 and is intended for filing, tracking and processing of applications for various types of services rendered by the Central Drugs Standard Control Organization (CDSCO) of India. The latest phase includes modules for manufacturing facilities, approved pharmaceutical products as well as retail and wholesale licences.
► CDSCO. Notice, 3 April 2017.

### Ingredients catalogue in Australia

**Australia** – The TGA has published an online catalogue of ingredients approved for use in listed medicines. The catalogue provides a single, searchable online source of information on excipients and associated requirements, increasing transparency for industry and consumers and reducing complexities for business. The catalogue is can be accessed through the Ingredient Table search facility on the TGA’s Business Services website.
► TGA News, 4 April 2017.
TGA Business Services website.
Under discussion

European Union – The EMA has published draft guidance on the type and format of data on antimicrobial use by animal species. The guidance is intended for EU member states that might provide such data to EMA from their national data collection systems on a voluntary basis.

► EMA Consultation, 24 March 2017.
Closing date: 24 September 2017.

Health Canada is proposing regulations that would make a warning sticker and patient information handout mandatory with all prescription opioids at the time of sale. Final publication of the regulations would mark the first time the Canadian government requires a warning sticker and patient handout with a dispensed medicine.

Closing date: 31 August 2017.

The EMA has released a draft guideline outlining the practical arrangements for notification of serious breaches of clinical trials authorized in the EU. It aims to provide advice on what should be classified as a serious breach and what should be reported.

► EMA Consultation, 23 May 2017.
Closing date: 22 August 2017.

European Union – The EMA has proposed a concept paper to clarify the regulatory expectations for data to support the approval of novel medicines to treat influenza. Several new antiviral agents are being developed for this indication.

► EMA Consultation, 4 May 2017.
Closing date: 31 July 2017.

Canada – The Government of Canada has launched a consultation on proposed amendments to the Patented Medicines Regulations. The amendments are intended to provide new regulatory tools and information to protect Canadian consumers from high prescription drug prices.

Closed 28 June 2017.

United States of America – The FDA has solicited input on its proposal for the future of patient engagement so that the perspectives of patient communities can be better captured. For this purpose the Agency is considering to establish a new Office of Patient Affairs.

► FDA Notice in the Federal Register, 14 March 2017.
Closed 12 June 2017.

London, UK – The EMA has released a concept paper on the need for revision of its guidance on the quality of water for pharmaceutical use. The guideline was originally adopted in 2002.

► EMA Consultation, 6 March 2017.
Closed 6 June 2017.

United States of America – The FDA has extended the period for comments on its draft guidance on the data and information
expected for a **biological product** to meet the standard for **interchangeability**.

- **FDA Docket ID:** FDA-2017-D-0154. **Docket folder summary.**
  - Extended until 19 May 2017.

**Australia** – The TGA has released a consultation document on proposed options for the future regulation of so-called **“low risk” products**, such as antiperspirants, over-the-counter (OTC) products, disinfectants, sunscreens, class I medical devices, vitamins and minerals, and homeopathic products.

- **TGA Consultation, 31 March 2017.**

The TGA has also informed the public about a new notifications process to be introduced for **“very low risk” variations** of registered medicines.

- **Notifications process: requests to vary registered medicines where quality, safety and efficacy are not affected.** Version 1.0, June 2017 (pending legislative amendments). 8 June 2017.

**Canada** – Health Canada has proposed to permit **emergency imports** of bulk quantities of foreign-authorized medications, *i.e.* medications that have been authorized in the U.S., the EU or Switzerland, but not yet in Canada. The permits would be valid for one year, renewable. The most immediate need is expected to be for medicines to treat opioid use disorder.

- **Health Canada News release, 21 April 2017.**
  - Comment period: 15 days.

**Australia** – The TGA has invited comments from interested parties on its proposed **provisional approval registration process** and post-market requirements for provisionally registered medicines. This follows a recommendation from the Review of Medicines and Medical Devices regulation to implement expedited pathways in Australia.

A consultation paper on the proposed eligibility criteria and designation process for the two proposed expedited pathways (priority review and provisional approval) was published by the TGA in October 2016.

- **TGA Consultation, 20 March 2017.**
  - Closed 1 May 2017.

**Australia** – The TGA has sought comments on its proposed changes that will **strengthen safety monitoring** for medicines available in Australia. The changes will apply to medicines only and will be implemented progressively from late 2017 onward.

- **TGA Consultation, 20 March 2017.**
  - Closed 1 May 2017.

**India** – The Ministry of Health and Family Welfare has launched a public consultation on the development of an electronic platform for tracking the supply of medicines in India. All manufacturers, wholesalers and distributors will be required to register on this portal and enter batch numbers, quantities supplied and expiry dates of all medicines supplied, sold or returned to the manufacturers. This tracking system is intended to complement the bar coding, which has been introduced for export purposes.


**Canada** – The Government of Canada has proposed amendments to the Protecting Canadians from Unsafe Drugs Act (*Vanessa’s Law*). Under the amended regulations, Health Canada would be able to require companies to conduct new tests and studies. Companies would also have to notify Health Canada of any drug safety-related actions required by a regulator in another jurisdiction.

- **Health Canada Statement, 21 April 2017.**
Approved

**Naldemedine for constipation caused by opioids**
- **Product name:** Symproic®
- **Dosage form:** Tablet
- **Class:** Opioid antagonist
- **Approval:** FDA
- **Use:** Treatment of opioid-induced constipation in adults with chronic non-cancer pain.
- **Benefits:** Increase in number of spontaneous bowel movements, compared to placebo.
  - [FDA. Drug trials snapshot. Symproic.](#)

**Cerliponase alfa for a rare neurodegenerative disorder in children**
- **Product name:** Brineura®
- **Dosage form:** Solution for intracerebroventricular infusion
- **Class:** Enzyme replacement therapy; **ATC code:** A16AB
- **Approval:** EMA (marketing authorization under exceptional circumstances, accelerated assessment; orphan designation)
  - FDA (priority review, breakthrough therapy; orphan drug designation)
- **Use:** Treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease in children.
- **Benefits:** Ability to slow the progression of motor and language decline.
  - **Note:** This is the first EMA- and FDA-approved medicine for CLN2 disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency, a very rare neurodegenerative genetic disorder that usually leads to the death of the child between the ages of eight and twelve years.
  - [EMA Press release, 21 April 2017.](#)
  - [FDA News release, 28 March 2017.](#)

**Nonacog beta pegol for haemophilia B**
- **Product name:** Refixia®
- **Dosage form:** Powder and solvent for solution for injection
- **Class:** Recombinant coagulation factor IX;
  - **ATC code:** B02BD
- **Approval:** EMA (orphan designation)
- **Use:** Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia.
- **Benefits:** Ability to prevent and treat bleeding in patients with haemophilia B.
  - [EMA CHMP opinion, 23 March 2017.](#)

**Dupilumab for atopic dermatitis**
- **Product name:** Dupixent®
- **Dosage form:** Subcutaneous injection
- **Class:** Antibody binding to the interleukin-4 receptor alpha subunit (IL-4Ra) protein;
  - **ATC code (temporary):** D11AH05
- **Approval:** FDA (priority review, breakthrough therapy)
- **Use:** Treatment of adults with moderate to severe eczema (atopic dermatitis) not controlled adequately by topical therapies. Can be used with or without topical corticosteroids.
- **Benefits:** Greater efficacy than placebo to clear skin and reduce itch.
  - [FDA News release, 28 March 2017.](#)

**Abaloparatide for osteoporosis**
- **Product name:** Tymlos®
- **Dosage form:** Injection for subcutaneous use
- **Class:** Human parathyroid hormone related peptide analog
- **Approval:** FDA
- **Use:** Treatment of postmenopausal women with osteoporosis at high risk of fractures.
- **Benefits:** Ability to reduce the risk of vertebral and nonvertebral fractures.
  - **Safety information:** A dose-dependent increase in the incidence of osteosarcoma was found in animal studies. This medicine is not recommended in patients at increased risk for osteosarcoma. Cumulative use with other parathyroid hormone analogs for more than
Inotuzumab ozogamicin for acute lymphoblastic leukaemia

**Product name:** Besponsa®
**Dosage form:** Powder for concentrate for solution for infusion
**Class:** Specific humanised immunoglobulin class G subtype 4 (IgG4) antibody; **ATC code:** L01XC26
**Approval:** EMA (orphan designation)
**Use:** Treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia.
**Benefits:** Ability to increase the proportion of patients who have complete remission and molecular remission and to delay the progression of disease.

Durvalumab for bladder cancer

**Product name:** Imfinzi®
**Dosage form:** Injection for intravenous use
**Class:** Programmed death-ligand 1 (PD-L1) blocking antibody; **ATC code (temporary):** L01XC28
**Approval:** FDA (accelerated approval, priority review, breakthrough therapy)
**Use:** Treatment of patients with locally advanced or metastatic urothelial carcinoma not responding, or no longer responding, to platinum-containing chemotherapy.
**Benefits:** Ability to shrink tumours in approx. 17% of patients treated.
► FDA web post, 1 May 2017.

Midostaurin for acute myeloid leukaemia

**Product name:** Rydapt®
**Dosage form:** Capsules
**Class:** Kinase inhibitor; **ATC code:** L01XE39

**Approval:** FDA, fast track designation (for the AML indication), priority review (for the mastocytosis indication), breakthrough therapy
**Uses:**
- Treatment of newly diagnosed, FLT3 mutation-positive acute myeloid leukaemia (AML), in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.
- Treatment of aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasm, or mast cell leukaemia.
**Benefits:** In AML: longer survival and longer progression-free survival period than with chemotherapy alone (a specific median survival rate could not be reliably estimated).

Ribociclib for breast cancer

**Product name:** Kisqali®
**Dosage form:** Tablets
**Class:** Cyclin-dependent kinase 4/6 inhibitor; **ATC code (temporary):** L01XE42
**Approval:** FDA (breakthrough therapy, priority review)
**Use:** In combination with an aromatase inhibitor as initial endocrine-based therapy, treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.
**Benefits:** Improvement in investigator-assessed progression-free survival. Overall survival data are immature.
**Safety information:** Ribociclib can cause QT interval prolongation, hepatobiliary toxicity, neutropenia, and harm to an unborn child.

Brigatinib for certain lung cancers

**Product name:** Alunbrig®
**Dosage form:** Tablets
Approved

Class: Tyrosine kinase inhibitor;  
ATC code (temporary): L01XE43

Approval: FDA (accelerated approval)

Use: Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib.

Benefits: Ability to shrink tumours in approximately half of the patients enrolled in the clinical study.

► FDA Prescribing information, April 2017.
Available from: Drugs@FDA: FDA Approved Drug Products

Niraparib for certain recurrent cancers

Product name: Zejula®
Dosage form: Capsules

Class: Poly ADP-ribose polymerase (PARP) inhibitor; ATC code (temporary): L01XX54

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

Use: Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, whose tumours have completely or partially shrunk in response to platinum-based chemotherapy.

Benefits: Longer progression-free survival than with placebo.


Ocrelizumab for multiple sclerosis

Product name: Ocrevus®
Dosage form: Intravenous infusion

Class: Selective immunosuppressant; ATC code: L04AA36

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


Benefits: Longer time to the worsening of disability, compared to placebo.

Safety information: Ocrelizumab should not be given to patients with active hepatitis B virus infection.

Notes: This is the first FDA-approved treatment of primary progressive multiple sclerosis. Ocrelizumab is also under review by EMA (1) and Health Canada. (2)

(1) EMA. Applications for new human medicines under evaluation by the Committee for Medicinal Products for Human Use. March 2017.

Sarilumab for rheumatoid arthritis

Product name: Kevzara®
Dosage form: Solution for subcutaneous injection

Class: Interleukin inhibitor, specific human monoclonal antibody (IgG1 subtype); ATC code: L04AC14

Approval: EMA

Use: Treatment of moderately to severely active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).

Benefits: Ability to reduce the signs and symptoms of rheumatoid arthritis and to improve physical function.


Avelumab for rare skin cancer

Product name: Bavencio®
Dosage form: Injection

Class: Programmed death ligand-1 (PD-L1) blocking antibody

Approval: FDA (accelerated approval, priority review, breakthrough therapy; orphan designation)

Use: Treatment of adults and children 12 years and older with metastatic Merkel cell carcinoma.

Benefits: Ability to shrink tumours in approx. 33% of patients treated.

Note: This is the first FDA-approved treatment option for metastatic Merkel cell carcinoma.

Approved

**Autologous chondrocyte suspension** to repair cartilage defects in the knee

**Product name:** Spherox®
**Dosage form:** Implant suspension
**Class:** Autologous chondrocytes;  
**ATC code:** M09AX02
**Approval:** EMA

**Use:** Repair of certain cartilage defects of the knee.

**Benefits:** Ability to repair symptomatic cartilage defects in the knee with defect sizes up to 10 cm².

**Notes:** This is an advanced therapy medicinal product in the form of a suspension containing 10–70 three-dimensional spheroids/cm², each composed of a cartilage matrix with the patient’s own chondrocytes, isolated from healthy cartilage and cultured in vitro. The CHMP positive opinion was based on an assessment by the Committee for Advanced Therapies.


**Edaravone** for amyotrophic lateral sclerosis

**Product name:** Radicava®
**Dosage form:** Intravenous infusion
**Class:** Free radical scavenger
**Approval:** FDA (orphan drug designation)

**Use:** Treatment of patients with amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease.

**Benefits:** Ability to slow the decline of daily functioning.

**Notes:** This is the second FDA-approved medicine for ALS, after riluzole, which gained FDA approval in 1995. Edaravone was previously approved in Japan.


**Valbenazine** for tardive dyskinesia

**Product name:** Ingrezza®
**Dosage form:** Capsules
**Class:** Vesicular monoamine transporter 2 (VMAT2) inhibitor

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

**Use:** Treatment of adult patients with tardive dyskinesia, a neurological disorder characterized by repetitive involuntary movements seen in some patients treated with certain medications.

**Benefits:** Ability to reduce the severity of involuntary movements, compared with placebo.


**Deutetrabenazine** for chorea

**Product name:** Austedo®
**Dosage form:** Tablets
**Class:** Vesicular monoamine transporter 2 (VMAT2) inhibitor

**Approval:** FDA

**Use:** Treatment of chorea associated with Huntington’s disease.

**Benefits:** Ability to reduce chorea in Huntington’s disease patients.

**Safety information:** This medicine increases the risk of depression and suicidal thoughts. It is contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression.

► FDA. Drug trials snapshots: Austedo.

**Triple combination for COPD**

**Product name:** Trimbow®
**Dosage form:** Solution delivered by pressurized metered dose inhaler
**Class:** Triple combination of an inhaled glucocorticoid (beclometasone dipropionate), a long-acting beta-2 receptor agonist (formoterol fumarate dihydrate) and a long-acting muscarinic antagonist (glycopyrronium bromide). ATC code: R03AL09

**Approval:** EMA

**Use:** Maintenance treatment of moderate to severe chronic obstructive pulmonary disease (COPD).

**Benefits:** The product can relieve and prevent symptoms such as shortness of breath,
Approved

wheezing and cough and reduce exacerbations of COPD symptoms.

Cenegermin for a rare eye disease
Product name: Oxervate®
Dosage form: Eye drops solution
Class: Recombinant form of human nerve growth factor
Approval: EMA (accelerated assessment; orphan designation)
Use: Treatment of moderate or severe neurotrophic keratitis in adults
Benefits: Cenegermin can stimulate corneal healing and restore eye surface integrity in patients with neurotrophic keratitis suffering from persistent epithelial defects or corneal ulcers.
Notes: Neurotrophic keratitis is a rare eye disease that can lead to loss of sight. It is caused by damage to the trigeminal nerve, resulting in reduced sensation in the cornea and reduced production of substances that play a role in repairing damage and ensuring survival of cornea cells.

(2) MHRA. Decision, 7 June 2017.

Biosimilars

Insulin lispro
Product name: Insulin lispro Sanofi®
Reference product: Humalog®
Approval: EMA
Use: Treatment of diabetes mellitus.

Rituximab

Product name: Rixathon®
Reference product: Mabthera®
Approval: EMA
Use: Treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis.

Etanercept

Product name: Erelzi®
Reference product: Enbrel®
Approval: EMA
Use: Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial
spondyloarthritis, plaque psoriasis and paediatric plaque psoriasis.

**Infliximab**

**Product name:** Renflexis® (infliximab-abda)

**Reference product:** Remicade®

**Approval:** FDA

**Use:** Treatment of Crohn's Disease, paediatric Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis.

► Drugs@FDA: FDA Approved Drug Products. Biologic License Application (BLA): 761054.

**Extensions of indications**

**Maraviroc for use in children**

**Product name:** Celsentri®

**Approval:** EMA

**Newly approved use:** Treatment of adolescents and children of 2 years of age and older and weighing at least 10 kg with certain types of HIV-1 infection.


**Sofosbuvir, ledipasvir and sofosbuvir for use in children and adolescents**

**Product name:**
- Sofosbuvir: Sovaldi®
- Ledipasvir/sofosbuvir: Harvoni®

**Approval:** FDA

**Newly approved use:** Treatment of certain types of hepatitis C virus infection in children 12 years of age and older or weighing at least 35 kg.


**Pembrolizumab for tumours with a certain biomarker**

**Product name:** Keytruda®

**Approval:** FDA (accelerated approval, priority review)

**Newly approved use:** Treatment of adults and children with unresectable or metastatic tumours having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), including:
- solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options and
- colorectal cancer that has progressed following treatment with certain chemotherapy drugs.

**Note:** This is the first FDA approval based on a tumour's biomarker without regard to the tumour's original location.


**Regorafenib for liver cancer**

**Product name:** Stivarga®

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

**Newly approved use:** Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib.

**Note:** This is the first FDA-approved treatment for liver cancer in almost a decade.


**Tocilizumab for giant cell arteritis**

**Product name:** Actemra®

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

**Newly approved use:** Treatment of giant cell arteritis, a form of vasculitis impeding adequate blood flow in the inflamed arteries.

**Note:** Tocilizumab was previously FDA-approved for certain types of arthritis. The newly approved indication provides the first FDA-approved therapy specific to this type of vasculitis.


**Ivacaftor to treat additional mutations of cystic fibrosis**

**Product name:** Kalydeco®

**Approval:** FDA
Extensions of indications

**Newly approved use:** Treatment of additional gene mutations in patients with cystic fibrosis.

**Note:** The approval triples the number of rare gene mutations that the drug can treat, from 10 to 33. The agency based its decision on the results of laboratory testing, in conjunction with evidence from earlier human clinical trials. This pathway was used because many cystic fibrosis mutations have such small patient populations that clinical trial studies are not feasible.


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**Early access**

**Glecaprevir/pibrentasvir for chronic hepatitis C infection**

**Dosage form:** Film-coated tablets

**Class:** Fixed-dose combination of two direct-acting antivirals

**Approval:** MHRA Early Access to Medicines Scheme (EAMS)

**Use:** Treatment of chronic hepatitis C virus (HCV) infection in adults. In the context of the EAMS, use of glecaprevir/pibrentasvir is restricted to certain patient groups.

**Benefits:** High cure rates of hepatitis C infection across HCV genotypes in patients with or without cirrhosis.

► MHRA EAMS. Decision, 10 May 2017.

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**EU ruling**

**Paracetamol/ibuprofen fixed-dose combination**

The EMA’s Committee for Medicinal Products for Human Use (CHMP) has concluded that marketing authorization can be granted for the analgesic fixed-dose combination paracetamol/ibuprofen 500mg/150mg film-coated tablets in relevant EU member states.

The matter had been referred to the CHMP because no agreement could be reached during joint assessment of the application under the EMA’s “Decentralized procedure”. The CHMP concluded that this combination is more effective than the individual components, while its safety profile is similar. Using the combination may avoid having to use stronger painkillers such as opioids, which have risks of abuse and misuse. Post-marketing data show that similar combinations have not led to significant long-term use (which is not authorized for this product) or increased safety concerns.

► EMA. Questions and answers on Paracetamol/ibuprofen 500mg/150mg film-coated tablets and associated names (tablets containing 500 mg paracetamol and 150 mg ibuprofen). 19 May 2017.
Publications and events

Access to medical products

Fair Pricing Forum
Amsterdam – The first Fair Pricing Forum was held in Amsterdam, the Netherlands, on 11 May 2017. The main objective of this Forum was to discuss options for a fairer pricing system that is sustainable for both health systems and innovation. The event was an initiative of WHO and was organized in collaboration with the Dutch Ministry of Health, Welfare and Sport. About 200 stakeholders from countries around the world came together to explore options to remedy essential medicines shortages that may be due to low profit margins, expand networks for exchange of experience, and identify research gaps specific to the current innovation and pricing system.

Background information about the challenges of the current system of setting prices for medicines is found in the report of the WHO Advisory Group meeting held in November 2016 in preparation for the event.

► WHO Essential medicines and health products. Fair pricing of medicines [webpage].

Information guide on biosimilars
Brussels – The EMA and the European Commission (EC) have published a new information guide for healthcare professionals, providing reference information on the science and regulation underpinning the use of biosimilars. (1) It complements earlier EC publications on biosimilars, including a guide for patients and a consensus information paper.

The guide was launched at the stakeholder conference on biosimilar medicines held in Brussels on 5 May 2017. The event was attended by representatives of patients, healthcare professionals, regulatory authorities, payers and the pharmaceutical industry. An updated report on the impact of biosimilar competition in Europe was also released at the conference. (2)

European Commission. Third stakeholder conference on biosimilar medicines [webpage].

WHO to pilot prequalification of biosimilars
Geneva – WHO has announced that it will launch a pilot project for prequalification of two biosimilar cancer medicines, rituximab and trastuzumab, in 2017. An invitation for expression of interest and submission of applications by manufacturers will be published in September. The WHO prequalification list is used by a wide range of national and international entities and thus promotes competitive pricing.

The decision to launch the pilot follows a two-day meeting between WHO, national regulators, pharmaceutical industry groups, patient and civil society groups, payers and policymakers. WHO also plans to explore options for prequalifying insulin.

To support the biosimilars prequalification pilot, WHO will review its 2009 Guidelines on the evaluation of similar biotherapeutic products. Furthermore the Organization will advocate for greater awareness of the benefits
and risks of biosimilars and will support the development of sustainable price-setting strategies for all biotherapeutics.


Updated Essential Medicines List

Geneva – WHO has published the 2017 update of its Essential Medicines Lists (EML) for adults and children. The list includes new advice on the use of antibiotics and 55 additional medicines, bringing the total to 433 medicines deemed essential for addressing the most important public health needs. The updates were recommended by the WHO Expert Committee on the Selection and Use of Essential Medicines at its 21st meeting, held on 27–31 March 2017.

For the first time, antibiotics used to treat 21 of the most common general infections have been grouped into three categories: “Access” (available at all times for a wide range of infections), “Watch” (first- or second-line treatments for a small number of infections) and “Reserve” (last-resort options for use in the most severe circumstances).

The advice supports WHO’s Global action plan on antimicrobial resistance.

Furthermore, the following medicines were added to the EML:

- 10 antibiotics for adults and 12 for children
- dasatinib and nilotinib for oral treatment of chronic myeloid leukaemia that has become resistant to standard treatment;
- sofosbuvir + velpatasvir as the first combination therapy to treat all six types of hepatitis C;
- dolutegravir for HIV infection;
- HIV pre-exposure prophylaxis (PrEP) with tenofovir alone, or in combination with emtricitabine or lamivudine;
- delamanid for children and adolescents, and clofazimine for children and adults with multidrug-resistant tuberculosis;
- child-friendly fixed-dose combination formulations of first-line anti-tuberculosis medicines,
- two artemisinin-based combination therapies (pyronaridine+artesunate and dihydroartemisinine+piperaquine) and a rectal artesunate formulation for young children, for the treatment of malaria; and
- fentanyl skin patches and methadone for pain relief in cancer patients.(1)

The Expert Committee further recommended to develop an Essential Diagnostics List (2).

(1) WHO News release, 6 June 2017.

WHO Model List of Essential Medicines. 20th List (March 2017).

WHO Model List of Essential Medicines for Children. 6th List (March 2017).

(2) WHO-EMP News, 15 June 2017.

MPP licence for investigational hepatitis C medicine

Amsterdam – The Medicines Patent Pool (MPP) and the Egyptian company Pharco Pharmaceuticals have signed a licence for the investigational medicine ravidasvir, a direct-acting antiviral (DAA) with the potential of working across all six major hepatitis C genotypes.

The new MPP licence expands the geographic scope of an earlier licence signed by the Drugs for Neglected Diseases initiative (DNDi) and Presidio, the original developer of ravidasvir. Combined, the MPP and DNDi agreements would benefit an area which is home to 85% of people living with hepatitis C in low- and middle-income countries.

Regulatory reforms in Mexico
A recent publication describes the implementation and impact of a multifaceted series of regulatory and legal reforms instituted by the Government of Mexico and the national medicines regulatory agency, COFEPRIS. The reforms aimed to facilitate the implementation of a new national access to medicines policy and to align the regulatory system with international standards. They encompassed administrative processes, clinical trials oversight, reliance on market authorization information and reports of other trusted regulators, and validation of activities by the Pan American Health Organization (PAHO) and WHO.

The paper shows that the reforms have increased the availability and affordability of safe, effective, quality medicines in the private and public sectors, and have facilitated expansion of the Mexican pharmaceutical industry. The regulatory optimization approach undertaken by Mexico could be a useful model for other countries that wish to facilitate access to needed quality medicines while encouraging local economic development.


Access to Vaccines Index 2017
Amsterdam – The Access to Medicines Foundation has published its first Access to Vaccines Index, the first publically available tool that maps how vaccine companies are responding to global calls to increase access to vaccines. The Index assesses eight key vaccine suppliers, and looks at their efforts to develop, manufacture and supply preventive vaccines for 69 high priority diseases across 107 high-need countries. The Index finds that the companies evaluated do this in a variety of ways depending on their diverse pipelines, portfolios and revenues.

The Access to Medicine Foundation published its first benchmark of industry activity in the 2008 Access to Medicine Index, which is now in its fifth iteration. The Foundation is also developing the first Antimicrobial Resistance Benchmark.


Reporting of clinical trial results
Geneva - Some of the world's largest funders of medical research and international non-governmental organizations have agreed on new standards that will require all clinical trials they fund or support to be registered, and the results to be disclosed publicly. New policies will be developed and implemented within the next 12 months. Most of these trials and their results will be accessible via WHO's International Clinical Trials Registry Platform.

Today, about half of all clinical trials go unreported, often because the results are negative. This leaves an incomplete and potentially misleading picture of the risks and benefits of vaccines, medicines and medical devices and can lead to use of suboptimal or even harmful products. The agreement means that the ethical principles laid down in the 2015 WHO position on public disclosure of results from clinical trials, which builds on the World Medical Association's 2013 Declaration of Helsinki, will now be enforced in thousands of trials every year.


WHO. International Clinical Trials Registry Platform (ICTRP) [website]. http://www.who.int/ictrp/en/
Safety evaluation and monitoring

Confirmatory clinical studies lacking

The outcomes of a systematic review show that post-market studies are not always conducted to confirm the expected benefits of medicines that gained regulatory approval based on limited evidence. The review characterized the prospective controlled clinical studies for novel drugs that were first approved by the U.S. FDA between 2005 and 2015 on the basis of limited evidence. It included 117 products approved on the basis of a single pivotal trial, pivotal trials that used surrogate markers of disease as primary endpoints, or both. The review found that the quantity and quality of post-approval clinical evidence varied substantially for these products, with few controlled studies published after approval that confirmed efficacy using clinical outcomes for the original FDA-approved indication. (1)

► Pease AM, Krumholz HM, Downing NS. Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review. BMJ 2017;357:j1680.

Importance of monitoring new drugs

A third of FDA-approved medicines have significant post-market safety events. In a recent study 71 of 222 novel therapeutics approved by the FDA in the period from 2001-2010 were affected by one or more significant event (withdrawal, “boxed warning” and/or safety communication). Products that gained accelerated approval were twice as likely to have postmarket safety events than other products. Safety events were also found to be more likely for biologicals, medicines to treat psychiatric conditions, and products approved near the regulatory deadline for approval.

These findings highlight the importance of continuous safety monitoring of medicinal products throughout their life cycle.


Medicines supply and use

New industry alliance to curb antimicrobial resistance

Berlin – The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) has announced the launch of the AMR Industry Alliance, which brings together research-based companies to drive and measure industry progress to curb antimicrobial resistance (AMR). The announcement was made at the B20 Health Conference in Berlin. The Alliance will ensure that signatories collectively deliver on the commitments made in the the Industry Declaration on AMR signed at the World Economic Forum in Davos in January 2016 and the AMR Roadmap. A reporting mechanism will be developed to track progress, identify gaps and set targets for the future.


Antibiotics consumption in eastern Europe and central Asia

A new report released by the WHO Regional Office for Europe sheds light on antibiotic consumption in eastern European and central Asian countries. The data were gathered through the WHO Antimicrobial Medicines Consumption (AMC) Network and include information from a number of non-EU countries.
The WHO AMC Network was established by the WHO Regional Office for Europe in 2011 to assist countries in setting up or strengthening national AMC surveillance and to contribute to region-wide AMC surveillance.


Off-label use of medicines in Europe
A new study describes the complex field of off-label use of medicinal products in the EU, i.e. the use of the products outside the terms approved as part of the marketing authorization under which a product can be used safely and effectively.

The study was conducted by the Netherlands institute for health services research (NIVEL), the Dutch National Institute for Public Health and the Environment (RIVM) and the European Public Health Alliance (epha) for the European Commission. Applying a wide range of methods, it provides information on the prevalence and incidence of off-label use and its drivers. It investigates the balance between the benefits and risks for patients and describes the national frameworks that govern the off-label use of medicinal products in EU Member States. The study shows how authorities have addressed the issue and how patients, healthcare professionals and industry react to this.


Combating medication errors
Geneva – WHO has launched a global initiative to reduce severe, avoidable medication-associated harm by 50% over the next five years. The Global Patient Safety Challenge on Medication Safety aims to improve the ways in which medicines are prescribed and distributed in health systems, and to increase awareness among patients about the risks associated with the improper use of medication.

Medication errors cause at least one death every day and injure approximately 1.3 million people annually in the United States of America alone. While low- and middle-income countries are estimated to have similar rates of medication-related adverse events to high-income countries, the impact is about twice as much in terms of the number of healthy life years lost. Globally, the cost associated with medication errors has been estimated at US$ 42 billion annually or almost 1% of total global health expenditure. Many countries lack good data, which will be gathered as part of the initiative.


Toolkit to protect supply chains
The Asia Pacific Economic Cooperation (APEC) has published an interactive PDF document to protect the medical product supply chains. (1). The document contains interactive links to recommended best practices and tools that can help to prevent and detect substandard and falsified medical products before they reach the consumer, and to efficiently respond to incidents. The document is the outcome of collaboration of ten work streams under the APEC Global Supply Chain Security and Integrity Roadmap project. It includes links to relevant tools and guidance provided by the WHO Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medical products.
and the WHO Global Surveillance and Monitoring System.

APEC. Supply chain security toolkit for medical products (PDF, 6.6 MB).

Disease updates

Poliomyelitis: Towards eradication

Geneva, Brazzaville, New York, Dakar – The largest-ever synchronized vaccination campaign of its kind was conducted in 13 countries across west and central Africa to tackle the threat of polio. All children under five years of age in Benin, Cameroon, Central African Republic, Chad, Côte d’Ivoire, Democratic Republic of Congo, Guinea, Liberia, Mali, Mauritania, Niger, Nigeria and Sierra Leone – were immunized with bivalent oral polio vaccine (bOPV).

The security-compromised areas in Borno state, north-eastern Nigeria, is widely considered to be the last remaining polio reservoir. Due to its epidemic-prone nature the virus could easily spread to under-protected areas of neighbouring countries. With the strong commitment of Africa’s leaders polio could now be eradicated.\(^{(1)}\)

In May 2017 the WHO Emergency Committee under the International Health Regulations concluded that polio remains a public health emergency of international concern, but that the world is now closer to polio eradication than ever before. The Committee’s temporary recommendations will be maintained for another 3 months, with some changes to the categories of countries subject to the recommendations.\(^{(2)}\)

(2) WHO Statement, 2 May 2017.

Depression: Leading cause of disability

Geneva – WHO has released its new estimates of the prevalence of depression and other mental disorders at the global and regional level, together with data concerning the consequences of these disorders in terms of lost health. More than 300 million people were living with depression in 2015, an increase of more than 18% since 2005.

On average, only 3% of government health budgets are invested in mental health. Fewer than half of people affected globally (and fewer than 10% in many countries) receive appropriate treatment. This is mainly because of a lack of resources and trained health care providers, and because of social stigma associated with mental disorders.

Depression increases the risk of substance use disorders and diseases such as diabetes and heart disease. Conversely, people with these conditions have a higher risk of depression. According to a WHO-led study, low levels of recognition and access to care for depression and anxiety cause economic losses of a trillion US dollars every year in total to households, employers and governments.


Neglected tropical diseases: Remarkable achievements

Geneva – The fourth WHO report on neglected tropical diseases shows that there is tremendous progress in some areas, but also much remaining to do. The report was released at the Global Partners’ Meeting on Neglected Tropical Diseases (NTDs) on 19 April 2017. The event marked ten years of multi-stakeholder collaboration and the
5th anniversary of the WHO NTD Roadmap and the London Declaration.

Remarkable achievements have been made in tackling lymphatic filariasis, onchocerciasis, Guinea-worm disease, African human trypanosomiasis, trachoma, visceral leishmaniasis and rabies. The report outlines four main areas that remain to be addressed. Firstly there is a need for investments to develop innovative disease prevention and management interventions. Secondly, vector control needs to be strengthened globally as it can prevent the transmission of many NTDs. A response plan for 2017–2030 was welcomed by the delegates at the Seventieth World Health Assembly. The WHO Prequalification team will play a crucial role in assessing the quality of long-lasting insecticide-treated bed nets, indoor residual spraying, space sprays and larvicides. Thirdly, public health measures must be intensified to combat zoonotic diseases, for example to ensure the availability of rabies vaccine meeting internationally accepted quality standards. Finally, safe water, sanitation and hygiene are critical in fighting NTDs, and measures to this effect will be part of the global plan.


Malaria: Push for prevention

Geneva, Nairobi – On World Malaria Day 2017 WHO has called for a faster scale-up of efforts to prevent malaria. Proven prevention approaches include insecticide-treated nets – which account for more than two thirds of cases prevented since 2001 – as well as indoor residual spraying with insecticides and preventive medicines for pregnant women, under-fives and infants. Across the Sahel, WHO also recommends malaria chemoprevention during the rainy season. The uptake of some of these measures needs to be accelerated, especially in Africa, which bears 90% of the global malaria burden.(1)

Brazzaville – The World Health Organization Regional Office for Africa (WHO/AFRO) has announced that Ghana, Kenya and Malawi will participate in a WHO-coordinated malaria vaccine pilot programme in selected areas, beginning in 2018. The vaccine under study, the RTS,S® vaccine, could be added to the current malaria control tools as a complementary preventive measure. The pilot will show whether the vaccine's protective effect in children aged 5–17 months shown in Phase III testing can be replicated in real life. Specifically, the pilot programme will assess the feasibility of delivering the required four doses of RTS,S®, the vaccine’s potential role in reducing childhood deaths, and its safety in the context of routine use. (2)


Hepatitis: Need for urgent global response

Geneva – A new WHO report describes, for the first time, the global and regional estimates on viral hepatitis in 2015. The data set the baseline for tracking progress in implementing the new global strategy endorsed by the World Health Assembly in 2016. The report highlights the urgency of closing the gaps in access to life-saving testing and treatment.

The report focuses on hepatitis B and C, which cause 96% of overall hepatitis mortality. An estimated 325 million people worldwide are living with chronic hepatitis B
or C virus infection. Mortality is increasing, with 1.34 million deaths in 2015.

For hepatitis B virus (HBV) new infections are falling thanks to increased vaccination coverage among children. HBV infection requires lifelong treatment, WHO currently recommends tenofovir for this purpose.

For hepatitis C virus (HCV) there is currently no vaccine available. Unsafe injections are considered to be the most common route of transmission. Approximately 1.75 million people were newly infected in 2015, bringing the global total of people living with HCV to 71 million. HCV infection can now be cured with the new direct-acting antiviral medicines (DAAs). Prices are falling but remain unaffordable in many countries.


Ebola: Response to new outbreak

A new outbreak of Ebola virus disease has been reported from the Democratic Republic of the Congo (DRC). The outbreak appears to be geographically relatively limited. WHO and partners are supporting the Ministry of Health in all aspects of the response, including epidemiological investigation, surveillance, logistics and supplies, communications and community engagement.

Following the official confirmation of the outbreak, Gavi, the Vaccine Alliance has stated that it stands ready to support the Government of the DRC in bringing the epidemic under control. A 2016 agreement between Gavi and Merck, the developer of the Ebola vaccine rVSV-ZEBOV, ensures that 300 000 vaccine doses are available for emergencies. The WHO and others will determine if and when deployment of vaccine in this outbreak is warranted.

Gavi, the Vaccine Alliance. Statement, 12 May 2017.

Upcoming events

Ireland to host 18th ICDRA
Dublin – Ireland has been confirmed as the location for the next International Conference of Drug Regulatory Authorities (ICDRA). The Conference will take place in Dublin on 3–7 September 2018. This biennial WHO-organized event provides regulatory authorities with a unique forum to meet and discuss ways to strengthen global collaboration in the area of medicines’ regulation in order to improve the quality, safety and efficacy of medicines globally.

► HPRA News, 19 April 2018.
WHO. International Conference of Drug Regulatory Authorities (ICDRA) [webpage].
www.who.int/medicines/icdra/en/

Joint manufacturers meeting

The 2017 joint UNICEF–UNFPA–WHO manufacturers meeting will take place in Copenhagen, Denmark, on 18–21 September 2017. The joint manufacturers meeting provides information for suppliers of medical products for use by UN agencies and other international organizations.

WHO Prequalification website. Events.
https://extranet.who.int/prequal/
WHO news

Seventieth World Health Assembly
Geneva — The Seventieth World Health Assembly was held in Geneva on 22–31 May 2017. Delegates made decisions on a wide range of health-related issues, including WHO’s response to health emergencies, the International Health Regulations and Pandemic Influenza Preparedness. Important decisions were also taken relating to polio, antimicrobial resistance, access to medicines and vaccines, the health of refugees and migrants, improving vector control, adolescent health and chemicals management, as well as on noncommunicable diseases (NCD), including dementia, cancer – including access to affordable treatment – and preparations for the 2018 UN General Assembly High-Level Meeting on NCDs.

The Assembly approved the programme budget for the biennial period 2018–19, which includes a 3% increase in assessed member contributions. In past years, voluntary contributions – which are often tied to specific activities – have overtaken assessed contributions, providing the majority of WHO’s income.

► WHO Media centre. Seventieth World Health Assembly. Available at: www.who.int/mediacentre/events/2017/wha70

New WHO Director-General elected
Geneva — The Member States of WHO have elected Dr Tedros Adhanom Ghebreyesus as the Organization’s new Director-General. Prior to his election he served as Minister of Foreign Affairs of Ethiopia from 2012–2016 and as Minister of Health from 2005–2012. Dr Tedros has also served as chair of the Board of the Global Fund to Fight AIDS, Tuberculosis and Malaria; as chair of the Roll Back Malaria (RBM) Partnership Board; and as co-chair of the Board of the Partnership for Maternal, Newborn and Child Health.

Dr Tedros Adhanom Ghebreyesus will succeed Dr Margaret Chan, who has been WHO’s Director-General since 1 January 2007. He will begin his five-year term on 1 July 2017.


Medicines prequalification updates
1. The WHO Prequalification Team: medicines (PQTm) has prequalified the following “firsts”:
   • First sofosbuvir active pharmaceutical ingredient (API) – providing a quality source for generic manufacturers who wish to produce hepatitis C medicines.
   • First ethionamid dispersible tablet, a child-friendly formulation to treat tuberculosis.(1)
2. The following revised invitations for evaluation of products (“EOIs”) have been published:
   • 14th EOI for APIs;
   • 4th EOI for anti-hepatitis products;
   • 15th EOI for antimalarials; and
   • 15th EOI for HIV-related products.(2)
3. PQT-m has clarified its expectations regarding bioequivalence (BE) studies. On a trial basis, PQTm will consider prior scientific justification from applicants for the use of the reference-scaled approach for AUC acceptance criteria in BE studies for highly variable APIs.(3)

(2) WHO Prequalification of medicines. FPPs & APIs Eligible for Prequalification (“EOIs”).
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

Mebendazole tablets
(Mebendazoli compressi)

This is a draft proposal of a monograph for The International Pharmacopoeia (Working document QAS/16.685, March 2017).

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

**Category.** Anthelmintic.

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

**Additional information.** Strengths in the current WHO Model List of Essential Medicines (EML): 100 mg, 500 mg. Strengths in the current WHO EML for children: 100 mg, 500 mg.

**Requirements**

Comply with the monograph for Tablets.

**Definition.** Mebendazole tablets contain not less than 90.0% and not more than 110.0% of the amount of mebendazole (C\(_{16}\)H\(_{13}\)N\(_3\)O\(_3\)) stated on the label.

**Manufacture.** The formulation, manufacturing process and product packaging of mebendazole tablets are designed and controlled so as to minimize the conversion of the polymorphic form of mebendazole from C to A. They ensure that, at any stage of the life cycle of the product, when tested by a suitable method such as infrared spectrometry (see Identity test A) or X-ray powder diffractometry, the mebendazole in the tablets is predominantly in the form of polymorph C.
Identity tests

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

A. To a quantity of the powdered tablets containing 0.05 g of Mebendazole add 20 mL of water R, shake, filter and wash the residue with three quantities, each of 10 mL of water R. Dry the residue overnight under vacuum at room temperature and carry out the examination with the residue as described under 1.7 Spectrophotometry in the infrared region. The two infrared absorption bands at about 3405 cm\(^{-1}\) and 1720 cm\(^{-1}\) are concordant with those in the spectrum obtained from mebendazole RS (containing mebendazole polymorph C).

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 85 volumes of dichloromethane R, 5 volumes of methanol R, 5 volumes of acetone R and 5 volumes of anhydrous formic acid R as the mobile phase. Apply separately to the plate 5 μL of each of the following solutions. For solution (A) add 2 mL of formic acid R to a quantity of the powdered tablets containing 20 mg of mebendazole and sonicate for about 5 minutes. Add 18 mL of acetone R, mix, filter and use the filtrate. For solution (B) dissolve 10 mg of mebendazole RS in 1 mL of formic acid R and shake. Add 9 mL of acetone R and mix. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm).

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

D. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions 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 mebendazole obtained with solution (2).

Related substances

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (10 cm × 4.6 mm) packed with base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3 μm).\(^1\)

Use the following conditions for gradient elution:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
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<tbody>
<tr>
<td>0–15</td>
<td>80 to 70</td>
<td>20 to 30</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>15–20</td>
<td>70 to 10</td>
<td>30 to 90</td>
<td>Linear gradient</td>
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<td>20–25</td>
<td>10</td>
<td>90</td>
<td>Isocratic</td>
</tr>
<tr>
<td>25–26</td>
<td>10 to 80</td>
<td>90 to 20</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>26–36</td>
<td>80</td>
<td>20</td>
<td>Isocratic re-equilibration</td>
</tr>
</tbody>
</table>

Operate with a flow rate of 1.2 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 250 nm. Maintain the column temperature at 40°C.

\(^1\) A HYPERSIL BDS C\(_{18}\) column has been found suitable.
Prepare as a solvent a mixture of 60 volumes of methanol R and 40 volumes of water R.

For solution (1) transfer a quantity of the powdered tablets, containing about 100 mg of mebendazole, accurately weighed, to a 100 mL volumetric flask. Add 30 mL of anhydrous formic acid R and sonicate for about 20 minutes. Dilute to volume with solvent mixture, mix and filter. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 20.0 mL with the solvent mixture. For solution (3) transfer 10 mg mebendazole RS to a 10 mL volumetric flask, add 5 mL of methanol R and 1 mL of sodium hydroxide (~40 g/L) TS solution, heat in a water bath at 60°C for 1 hour, cool to room temperature and adjust the solution to pH 7 with hydrochloric acid (~36.5 g/L) TS. Dilute with methanol R to volume and mix.

Inject 10 µL of solution (3). Use the chromatogram to identify the peak due to impurity A. The impurity is eluted at the relative retention of 0.4 with reference to mebendazole (retention time about 12 minutes).

The test is not valid unless in the chromatogram obtained with solution (3) the resolution between mebendazole and impurity A is at least 10.

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

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%).

**Dissolution**

*For 100 mg tablets.* Carry out the test as described under **5.5 Dissolution test for solid oral dosage forms** using 900 mL of hydrochloric acid (~3.65 g/L) TS as the dissolution medium and rotating the paddle at 75 revolutions per minute. At 120 minutes withdraw a sample of 10 mL of the dissolution medium through an in-line filter. Allow the filtered sample to cool to room temperature. Dilute 5.0 mL of the filtrate to 50.0 mL with the dissolution medium.

Determine the content of mebendazole (C\textsubscript{16}H\textsubscript{13}N\textsubscript{3}O\textsubscript{3}) in the medium by **1.14.4 High-performance liquid chromatography** using the conditions described under "Assay" and a suitable solution of mebendazole RS as a reference solution.

For each of the six tablets tested calculate the total amount of mebendazole (C\textsubscript{16}H\textsubscript{13}N\textsubscript{3}O\textsubscript{3}) in the medium using the declared content of C\textsubscript{16}H\textsubscript{13}N\textsubscript{3}O\textsubscript{3} in mebendazole RS. The amount in solution for each tablet is not less than 60% (Q) of the amount declared on the label.

*For 500 mg tablets.* Carry out the test as described under **5.5 Dissolution test for solid oral dosage forms** using 900 mL of a 1.0% solution of sodium dodecyl sulfate R in hydrochloric acid (~0.365 g/L) TS as the dissolution medium and rotating the paddle at 75 revolutions per minute. At 60 minutes withdraw a sample of 10 mL of the dissolution medium through an in-line filter. Allow the filtered sample to cool to room temperature. Dilute 1.0 mL of the filtrate to 50.0 mL with the dissolution medium.
Determine the content of mebendazole \((C_{16}H_{13}N_{3}O_{3})\) in the medium by 1.14.4 High-performance liquid chromatography using the conditions described under “Assay” and a suitable solution of mebendazole RS as a reference solution.

For each of the six tablets tested calculate the total amount of mebendazole \((C_{16}H_{13}N_{3}O_{3})\) in the medium using the declared content of \(C_{16}H_{13}N_{3}O_{3}\) in mebendazole RS. The amount in solution for each tablet is not less than 70% \((Q)\) of the amount declared on the label.

**Assay**

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column \((10 \text{ cm} \times 4.6 \text{ mm})\) packed with octadecylsilyl base-deactivated silica gel for chromatography R \((3 \mu\text{m}).2\)

As the mobile phase use a solution prepared as follows: dissolve 7.5 g of ammonium acetate R in 1000 mL of water R, mix and filter. Mix 750 mL of this solution with 250 mL of acetonitrile R.

Prepare as a solvent a mixture of 60 volumes of methanol R and 40 volumes of water R.

Prepare the following solutions. For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets, containing about 100 mg of mebendazole, accurately weighed, to a 100 mL volumetric flask. Add 30 mL of anhydrous formic acid and sonicate for about 20 minutes. Dilute to volume with solvent mixture, mix and filter. Dilute 5.0 mL of the filtrate to 100.0 mL with the solvent mixture. For solution (2) transfer 25.0 mg of mebendazole RS to a 25 mL volumetric flask, add 10 mL of the anhydrous formic acid R and sonicate to dissolve. Dilute to volume with the solvent mixture. Dilute 5.0 mL of this solution to 100.0 mL with the solvent mixture.

Operate with a flow rate of 1.2 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 250 nm.

Inject alternately 10 µL each of solutions (1) and (2).

Measure the areas of the peaks corresponding to mebendazole obtained in the chromatograms from solution (1) and (2) and calculate the percentage content of mebendazole \((C_{16}H_{13}N_{3}O_{3})\) in the tablets using the declared content of \(C_{16}H_{13}N_{3}O_{3}\) in mebendazole RS.

**Reagents to be established**

**Hydrochloric acid (~0.365 g/L) TS**

Hydrochloric acid (~250 g/L) TS, dilute with water to contain 0.365 g of HCl in 1000 mL.

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2 A HYPERSIL BDS C18 column has been found suitable.
Proposed revision of the monograph on

Capreomycin sulfate
(Capreomycini sulfas)

This is a draft revision of a monograph for *The International Pharmacopoeia* (Working document QAS/16.689, May 2017). It is proposed to revise the monograph as follows:

- add a new reference substance – Capreomycin sulfate for identification RS – suitable for identity tests A and B (identification by IR and TLC);
- add a note of the Secretariat with respect to ongoing discussions about the transition from microbiological to physicochemical assays for antibiotics;
- update the style of the monograph.

The working document with line numbers for commenting 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). In the online document changes from the current monograph are indicated in the text by *insert* or *delete*.

**Note from the Secretariat.** The user of the monograph should note that the monograph describes a chromatographic assay to determine if the concentrations of capreomycin IA, IB, IIA and IIB of a sample under investigation complies with the definition (see section definition). Other pharmacopoeias have the activity of the substance determined for assay by means of microbiological methods. A correlation between the concentration of IA, IB, IIA and IIB and the activity of the substance, determined with microbiological methods, has not been established yet.

<table>
<thead>
<tr>
<th>Component</th>
<th>R1</th>
<th>R2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capreomycin IA</td>
<td>OH</td>
<td>β-Lysyl</td>
</tr>
<tr>
<td>Capreomycin IB</td>
<td>H</td>
<td>β-Lysyl</td>
</tr>
<tr>
<td>Capreomycin IIA</td>
<td>OH</td>
<td>H</td>
</tr>
<tr>
<td>Capreomycin IIB</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Capreomycin (base)</th>
<th>IA</th>
<th>IB</th>
<th>IIA</th>
<th>IIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
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<td>$C_{25}H_{44}N_{10}O_{7}$</td>
<td>$C_{19}H_{32}N_{12}O_{7}$</td>
<td>$C_{19}H_{32}N_{12}O_{6}$</td>
</tr>
<tr>
<td>Relative molecular mass</td>
<td>668.7</td>
<td>652.7</td>
<td>540.5</td>
<td>524.5</td>
</tr>
<tr>
<td>CAS Reg. no.</td>
<td>37280-35-6</td>
<td>33490-33-4</td>
<td>62639-89-8</td>
<td>62639-90-1</td>
</tr>
<tr>
<td>Theoretical value of $n$ in neutral sulfate salt</td>
<td>2</td>
<td>2</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Chemical names

Capreomycin IA: sulfate salt of \(([(Z)((3S,9S,12S,15S)-15\text{-amino-3-}\[(4R)-2\text{-amino-1,4,5,6-tetrahydropyrimidin-4-yl}]9-\{((3S)-3,6\text{-diaminohexanoyl}\text{amino})\text{methyl}\}-12\text{-}(\text{hydroxymethyl})-2,5,8,11-14\text{-pentaaxo-1,4,7,10,13\text{-pentaazacyclohexadecan-6-ylidene}}\text{methyl}]\text{urea})\].

Capreomycin IB: sulfate salt of \([Z](3S,9S,12S,15S)-15\text{-amino-3-}\[(4R)-2\text{-amino-1,4,5,6-tetrahydropyrimidin-4-yl}]9-\{((3S)-3,6\text{-diaminohexanoxy})\text{amino}\}\text{methyl]-12-methyl-2,5,8,11-14-pentaaxo-1,4,7,10,13\text{-pentaazacyclohexadecan-6-ylidene}\text{methyl}]\text{urea}].

Capreomycin IIA: sulfate salt of \([Z](3S,9S,12S,15S)-15\text{-amino-9-(aminomethyl)-3-}\[(4R)-2\text{-amino-1,4,5,6-tetrahydropyrimidin-4-yl}]12\text{-}(\text{hydroxymethyl})-2,5,8,11-14\text{-pentaaxo-1,4,7,10,13\text{-pentaazacyclohexadecan-6-ylidene}methyl}]\text{urea}].

Capreomycin IIB: sulfate salt of \([Z](3S,9S,12S,15S)-15\text{-amino-9-(aminomethyl)-3-}\[(4R)-2\text{-amino-1,4,5,6-tetrahydropyrimidin-4-yl}]12\text{-methyl-2,5,8,11-14-pentaaxo-1,4,7,10,13\text{-pentaazacyclohexadecan-6-ylidene}methyl}]\text{urea}].

CAS Reg. no. 1405-37-4 (for capreomycin sulfate).

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

**Solubility.** Very soluble in water, practically insoluble in ethanol (~750 g/L) TS and in ether.

**Category.** Antituberculosis drug.

**Storage.** Capreomycin sulfate should be kept in a tightly closed container or, if sterile, in a hermetically closed container.

**Labelling.** The label states, where applicable:

1. that the substance is free from bacterial endotoxins;
2. that the substance is sterile.

**Requirements**

**Definition.** Capreomycin sulfate is a mixture of the sulfates of antimicrobial polypeptides produced by the growth of Streptomyces capreolus. It contains not less than 70.0% of capreomycin, calculated with reference to the dried substance and taking into account the sum of capreomycin IA, IB, IIA and IIB. The content of capreomycin IA and IB is not less than 90.0% of the sum of capreomycin IA, IB, IIA and IIB.

**Identity tests**

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

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

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R5 as the coating substance and a mixture of 30 volumes of phenol R, 10 volumes of water R and 1 volume of ammonia (~260 g/L) TS as the mobile phase. Apply separately to the plate 4 μL of each of the following two solutions in water R. For solution (A) use 10 mg of the test substance per mL and for solution (B) use 10 mg of capreomycin sulfate for identification.
RS per mL. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air. Spray with triketohydrindene/methanol TS and heat the plate for 3 minutes at 120°C. Examine the chromatogram in daylight.

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

C. The absorption spectrum of a 20 µg/mL solution of the test substance in hydrochloric acid (0.1 mol/L) VS, when observed between 230 nm and 350 nm, exhibits a maximum at about 268 nm.

D. The absorption spectrum of a 20 µg/mL solution of the test substance in sodium hydroxide (0.1 mol/L) VS, when observed between 230 nm and 350 nm, exhibits a maximum at about 287 nm.

E. A 20 mg/mL solution of the test substance yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

pH value. pH of a 30 mg/mL solution of the test substance in carbon-dioxide-free water R, 4.5–7.5.

Loss on drying. Dry for 4 hours at 100°C under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury); it loses not more than 100 mg/g.

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 30 µg/g.

Sulfated ash. Not more than 10.0 mg/g.

Bacterial endotoxins. If intended for use in the manufacture of a parenteral dosage form, carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 0.5 IU of endotoxin per mg of capreomycin sulfate.

Sterility. If intended for use in the manufacture of either a parenteral or other sterile dosage form without a further appropriate sterilization procedure, complies with 3.2 Test for sterility.

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 A as diluent. For solution (1) use 2.0 mg of the test substance per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration of 10 µg of capreomycin sulfate per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 268 nm.

Inject 20 µL of solution (1). The test is not valid unless the resolution between the two major peaks corresponding to capreomycin IA (with a relative retention of about 0.89) and capreomycin IB (retention time about 38 minutes) is at least 2.0 and the resolution between the peaks corresponding to capreomycin IIA and capreomycin IIB (with a relative retention of 0.53 and 0.63, respectively) is at least 3.5.

Inject separately 20 µL each of solutions (1) and (2).
In the chromatogram obtained with solution (1) the area of any peak, other than the four major peaks corresponding to capreomycin IA, IB, IIA and IIB, is not greater than 4 times the sum of the areas of the four major peaks obtained with solution (2) (2.0%). The area of not more than one such peak is greater than twice the sum of the areas of the four major peaks obtained with solution (2) (1.0%). The sum of the areas of all peaks, other than the four major peaks, is not greater than 14 times the sum of the areas of the four major peaks obtained with solution (2) (7.0%). Disregard any peak with an area less than 0.1 times the sum of the areas of the four major peaks in the chromatogram obtained with solution (2) (0.05%).

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

The mobile phases for the gradient elution consist of a mixture of mobile phase A and mobile phase B, using the following conditions:
- mobile phase A: 5 volumes of acetonitrile R and 95 volumes of phosphate buffer pH 2.3;
- mobile phase B: 15 volumes of acetonitrile R and 85 volumes of phosphate buffer pH 2.3.

Prepare the phosphate buffer pH 2.3 by dissolving 54.4 g of potassium dihydrogen phosphate R in 1500 mL of water R, adjust the pH to 2.3 by adding phosphoric acid (~105 g/L) TS, add 9.4 g of sodium hexanesulfonate R and dilute to 2000 mL with water 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>0–25</td>
<td>55–52</td>
<td>45–48</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>25–40</td>
<td>52</td>
<td>48</td>
<td>Isocratic</td>
</tr>
<tr>
<td>40–60</td>
<td>30</td>
<td>70</td>
<td>Isocratic</td>
</tr>
<tr>
<td>60–70</td>
<td>55</td>
<td>45</td>
<td>Isocratic re-equilibration</td>
</tr>
</tbody>
</table>

Prepare the following solutions using mobile phase A as diluent. For solution (1) use 2.0 mg of the test substance per mL. For solution (2) use 2.0 mg of capreomycin sulfate RS per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 268 nm.

Inject 20 μL of solution (1). The assay is not valid unless the resolution between the two major peaks corresponding to capreomycin IA (with a relative retention of 0.89) and capreomycin IB (retention time about 38 minutes) is at least 2.0 and the resolution between the peaks corresponding to capreomycin IIA and capreomycin IIB (with a relative retention of 0.53 and 0.63, respectively) is at least 3.5.

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

Measure the areas of the peak responses for capreomycin IA, IB, IIA and IIB obtained in the chromatograms from solutions (1) and (2) and, using the sum of the areas, calculate the percentage content of capreomycin using the declared content in capreomycin sulfate RS.
Proposed revision of the monograph on

Capreomycin for injection
(Capreomycini ad injectionem)

This is a draft revision of a monograph for The International Pharmacopoeia
(Working document QAS/16.690, May 2017). It is proposed to revise the monograph as follows:
• add a new reference substance - Capreomycin sulfate for identification RS - suitable for identity test A and B (identification by IR and TLC);
• add a note of the Secretariat with respect to ongoing discussions about the transition from microbiological to physicochemical assays for antibiotics;
• determine the percentage content of capreomycin per sealed container;
• update the style of the monograph.

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects. In the online document changes from the current monograph are indicated in the text by insert or delete.

[Note from the Secretariat. The user of the monograph should note that the monograph describes a chromatographic assay to determine if the concentrations of capreomycin IA, IB, IIA and IIB of a sample under investigation complies with the definition (see section definition). Other pharmacopoeias have the activity of the substance determined for assay by means of microbiological methods. A correlation between the concentration of IA, IB, IIA and IIB and the activity of the substance, determined with microbiological methods, has not been established yet.]

Description. A white or almost white powder.

Category. Antituberculosis drug.

Storage. Capreomycin for injection should be stored in a well-closed container.

Labelling. The designation on the container of capreomycin for injection should state that the active ingredient is in the sulfate form and the quantity should be indicated in terms of the equivalent amount of capreomycin.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML): 1 g. Strength in the current EML for children: 1 g.

The injection is reconstituted by dilution of Capreomycin powder for injections in Water for injections.

The reconstituted injection should be used immediately after preparation.
Requirements

The powder for injection and the reconstituted injection comply with the monograph for Parenteral preparations.

Definition. Capreomycin for injection is a sterile powder containing Capreomycin sulfate. It contains not less than 90.0% and not more than 115.0% of the amount of capreomycin stated on the label, taking into account the sum of capreomycin IA, IB, IIA and IIB.

Identity tests

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

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region.

The infrared absorption spectrum is concordant with the spectrum obtained from capreomycin sulfate for identification RS or with the reference spectrum of capreomycin sulfate.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R5 as the coating substance and a mixture of 30 volumes of phenol R, 10 volumes of water R and 1 volume of ammonia (~260 g/L) TS as the mobile phase. Apply separately to the plate 4 µL of each of the following two solutions in water R. For solution (A) dissolve a quantity of the powder to obtain a solution containing 10 mg of the powder for injection per mL. For solution (B) use 10 mg of capreomycin sulfate for identification RS per mL. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air. Spray with triketohydridene/methanol TS and heat the plate for 3 minutes at 120°C. Examine the chromatogram in daylight.

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

C. Dissolve a quantity of the powder for injection in hydrochloric acid (0.1 mol/L) VS to obtain a solution containing the equivalent of 20 µg of capreomycin per mL. The absorption spectrum (1.6) of this solution, when observed between 230 nm and 350 nm, exhibits a maximum at about 268 nm.

D. Dissolve a quantity of the powder for injection in sodium hydroxide (0.1 mol/L) VS to obtain a solution containing the equivalent of 20 µg of capreomycin per mL. The absorption spectrum (1.6) of this solution, when observed between 230 nm and 350 nm, exhibits a maximum at about 287 nm.

E. A solution of the powder for injection containing the equivalent of 20 mg of capreomycin per mL yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

Clarity of solution. A freshly prepared solution of the powder for injection containing the equivalent of 1 g of capreomycin in 10 mL of carbon-dioxide-free water R is clear.

pH value (1.13). pH of a solution of the powder for injection containing the equivalent of 0.3 g of capreomycin in 10 mL of carbon-dioxide-free water R, 4.5–7.5.

Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 0.35 IU of endotoxin per mg of capreomycin.
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 A as diluent. For solution (1) dissolve a quantity of the powder for injection to obtain a solution containing the equivalent of 2.0 mg of capreomycin per mL. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration of 10 µg of capreomycin per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 268 nm.

Inject 20 µL of solution (1). The test is not valid unless the resolution between the two major peaks corresponding to capreomycin IA (with a relative retention of about 0.89) and capreomycin IB (retention time about 38 minutes) is at least 2.0 and the resolution between the peaks corresponding to capreomycin IIA and capreomycin IIB (with a relative retention of 0.53 and 0.63, respectively) is at least 3.5.

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

In the chromatogram obtained with solution (1) the area of any peak, other than the four major peaks corresponding to capreomycin IA, IB, IIA and IIB, is not greater than 4 times the sum of the areas of the four major peaks obtained with solution (2) (2.0%). The area of not more than one such peak is greater than twice the sum of the areas of the four major peaks obtained with solution (2) (1.0%). The sum of the areas of all peaks, other than the four major peaks, is not greater than 14 times the sum of the areas of the four major peaks obtained with solution (2) (7.0%). Disregard any peak with an area less than 0.1 times the sum of the areas of the four major peaks in the chromatogram obtained with solution (2) (0.05%).

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

The mobile phases for the gradient elution consist of a mixture of mobile phase A and mobile phase B using the following conditions:

- Mobile phase A: 5 volumes of acetonitrile R and 95 volumes of phosphate buffer pH 2.3;
- Mobile phase B: 15 volumes of acetonitrile R and 85 volumes of phosphate buffer pH 2.3.

Prepare the phosphate buffer pH 2.3 by dissolving 54.4 g of potassium dihydrogen phosphate R in 1500 mL of water R, adjust the pH to 2.3 by adding phosphoric acid (~105 g/L) TS, add 9.4 g of sodium hexanesulfonate R and dilute to 2000 mL with water R.

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<tr>
<td>60–70</td>
<td>55</td>
<td>45</td>
<td>Isocratic re-equilibration</td>
</tr>
</tbody>
</table>
Weigh and mix the contents of 5 containers. Prepare the following solutions using mobile phase A as diluent. For solution (1) dissolve a quantity of the mixed contents, containing the equivalent of about 100 mg of capreomycin, accurately weighed, and dilute to 50.0 mL. For solution (2) use a solution containing 2.75 mg of capreomycin sulfate RS per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 268 nm.

Inject 20 μL of solution (1). The assay is not valid unless the resolution between the two major peaks corresponding to capreomycin IA (with a relative retention of 0.89) and capreomycin IB (retention time about 38 minutes) is at least 2.0. and the resolution between the peaks corresponding to capreomycin IIA and capreomycin IIB (with a relative retention of 0.53 and 0.63, respectively) is at least 3.5.

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

Measure the areas of the peak responses for capreomycin IA, IB, IIA and IIB obtained in the chromatograms from solutions (1) and (2) and, using the sum of the areas, calculate the percentage content of capreomycin per sealed container using the declared content in capreomycin sulfate RS.

***
Transition from microbiological to physicochemical assays in monographs on capreomycin active pharmaceutical ingredients and products

This is a concept paper (Working document QAS/16.695, April 2017) proposed by the Secretariat of The International Pharmacopoeia.

The strength of antibiotics can be determined using microbiological or physicochemical assays. While traditionally microbiological methods were predominantly used in quality control of antibiotics, physicochemical methods are nowadays preferred for various reasons. The transition from microbiological to physicochemical assays has been largely completed for single-component antibiotics. For multicomponent antibiotics, however, the use of physicochemical methods remains challenging.

Following discussions and decisions at meetings of the WHO Expert Committees on Specifications for Pharmaceutical Preparations and on Biological Standardization, the Secretariat of The International Pharmacopoeia is seeking information and international collaboration in order to establish a chromatographic assay as an alternative to microbiological assays for the essential medicine capreomycin powder for injection and the corresponding active pharmaceutical ingredient (API) capreomycin sulfate. In addition, this initiative aims at harmonizing quality control requirements for these products. It may also provide new insights which can facilitate transitions of other antibiotics.

The Secretariat of The International Pharmacopoeia invites stakeholders, in particular regulatory authorities, pharmacopoeias and manufacturers of capreomycin sulfate, capreomycin powders for injection and other medicines containing multicomponent antibiotics, to comment on the proposals made in this document. Subsequent steps, in particular the performance of a bridging study to link the mass with the activity of capreomycin, will be decided inter alia based on the discussions of the comments received.

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

Scope of the document

This document proposes steps to finish the transition of the tuberculostatic aminoglycoside capreomycin that has been started with the publication of chromatographic assay methods in the monographs on Capreomycin sulfate and Capreomycin powder for injection of The International Pharmacopoeia. In the course of the transition, factors that may pose a risk to the safety of patients shall be identified and controlled, in particular by means of two surveys: a landscape analysis of capreomycin APIs and products on the global market and a comparison
of national capreomycin reference substances. Besides, this proposal aims at the international harmonization of quality control requirements for capreomycin.

**Background information**

Antibiotics produced by fermentation often consist of complex mixtures of structurally related components with different activities. Microbiological methods were historically used to quantify the total activity of these mixtures. As evidence of their structure and composition increased, transitions from microbiological to physicochemical assays, in particular chromatographic methods, were possible and envisaged as they are often more discriminative and easier or faster to perform. Microbiological assays, on the other hand, measure the total (in vitro) activity of antibiotics against a reference microorganism, integrating all moieties that contribute to this effect.

While the transition from microbiological to physicochemical assays has been largely completed for single-component antibiotics, it remains challenging for substances containing several components.

**Discussions at meetings of WHO Expert Committees**

Points to consider when switching from biological to physicochemical assays were discussed at the meetings of the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) and the Expert Committee on Biological Standardization (ECBS) in 2007. In 2009, the ECSPP recommended that microbiological assays shall be replaced by, in particular, chromatographic methods, where possible and appropriate. Following this decision, chromatographic assays were elaborated and published as part of the monographs on Capreomycin sulfate and Capreomycin for injection in *The International Pharmacopoeia*.

Following the publication of these monographs, the comparability of analytical results gained with the new chromatographic assay method and with so far used microbiological assays was discussed. At the meetings of the ECSPP and ECBS in 2016 it was agreed that the Secretariat of *The International Pharmacopoeia* should contact manufacturers to obtain further information about the prevailing composition of capreomycin active pharmaceutical ingredient (API), methods used to determine the content of capreomycin powders for injection and information regarding a correlation between the mass and the microbiological activity of the antibiotic.

**Capreomycin for injection in the WHO Model List of Essential Medicines**

In the WHO Model List of Essential Medicines (EML) (19th Edition) the strength of capreomycin powder for injection is given as “1 g (as sulfate) in vial”. Considering that in the past pharmacopoeias described microbiological methods for the assay of capreomycin products, the information regarding the strength given in the EML should be interpreted as “capreomycin sulfate equivalent to the activity of 1 g capreomycin in vial”. This interpretation would correspond to the way the comparator product, Capastat®, is labelled, namely “Each vial contains the equivalent of 1 g capreomycin activity”.


The monographs on Capreomycin sulfate and Capreomycin for injection in *The International Pharmacopoeia*

Capreomycin is a mixture of four structurally related compounds, Capreomycin IA, IB, IIA and IIB with different specific activities. In the monograph on Capreomycin sulfate the active substance is defined on a mass basis: “Capreomycin sulfate is a mixture of the sulfates of antimicrobial polypeptides produced by the growth of *Streptomyces capreolus*. It contains not less than 70.0% of capreomycin, calculated with reference to the dried substance and taking into account the sum of capreomycin IA, IB, IIA and IIB. The contents of capreomycin IA and IB is not less than 90.0% of the sum of capreomycin IA, IB, IIA and IIB”.

The Chinese Pharmacopoeia (CP), the Indian Pharmacopoeia (IP) and the United States Pharmacopeia (USP) have similar requirements regarding the composition of Capreomycin sulfate. However, in these pharmacopoeias the capreomycin content of APIs and finished products is determined using microbiological methods.

In 1969, the specific activities of the isolated four main components were determined. The results of these investigations showed that there is a significant difference between the activities of components IA versus IB and I versus II. As the applied techniques to separate and purify substances have become more specific and efficient in past decades, WHO was advised to re-establish the data should succeeding decisions be based on them.

While the monograph on Capreomycin currently limits the capreomycin II contents to maximum 10%, the ratio between capreomycin IA and IB is not defined at present. Further information and guidance is sought regarding the relevance of such an additional limit with a view to ensure that products even with extreme differences in the IA and IB concentrations consistently comply or not comply with the different compendial assays.

**Capreomycin sulfate reference substances**

Subsequent to the publication of the capreomycin monographs, a reference substance, capreomycin sulfate ICRS Batch 1, was established for use according to the prescribed compendial tests. Following a comprehensive analytical characterization of the candidate material, a defined capreomycin base concentration per vial, expressed in mass units, was assigned to the standard to render it suitable, *i.e.* for assay by high performance liquid chromatography (HPLC).

The ECSPP released capreomycin sulfate ICRS Batch 1 at its meeting in 2016 with the following note in the leaflet: “*The International Chemical Reference Substance for capreomycin sulfate ICRS is intended to be used as described in The International Pharmacopoeia for assay by HPLC according to the monographs for capreomycin sulfate and capreomycin for injection. The substance is suitable to serve as a reference for the quantitative determination of the content of capreomycins IA, IB, IIA and IIB from the declared content in capreomycin sulfate RS. A correlation between the concentration of IA, IB, IIA and IIB and the activity of the substance, determined with microbiological methods, has not been established*.”
A Capreomycin WHO International Standard for Antibiotics (ISA) to define the activity of capreomycin in microbiological assays was established in 1968\(^1\) and discontinued in 2000 following an enquiry to determine whether there was a continued necessity for the standard.\(^2\) The reference substance served as a primary reference standard for pharmacopoeias to calibrate their national, secondary reference standards, subsequently used in routine laboratory tests and assays.

**Landscape analysis of capreomycin APIs and products on the global market**

The aim of this survey is to provide an overview on the composition of capreomycin APIs and products on the market. Together with information on the activity and toxicity of the different components, the results of the chromatographic analysis will help to evaluate the comparability of capreomycin products. Based on the results of this survey, additional limits regarding the chemical composition of capreomycin, in particular a limit to specify the ratio IA to IB, shall be discussed and implemented if need be.

To initiate the survey, WHO shall invite manufactures to share the following information and samples:

**Manufacturers of capreomycin or capreomycin sulfate:**

1. A sample of capreomycin or capreomycin sulfate (about 10 g), representative for the authorized manufacturing process, together with the certificate of analysis and the material safety data sheet.

2. A compilation of the specifications of the product together with a description of the methods used to determine them. For the methods to determine the content/strength and composition of the product the reference substance(s) used, the name(s) of the authorizing organization(s) and the declared strength(s) or assigned content(s) shall be indicated. In case chromatographic methods are used sample chromatograms shall also be submitted.

3. The outcome of investigations to correlate the total microbiological activity of capreomycin/capreomycin sulfate (or the activity of the components) with the mass concentration of the components (including information about the design of the performed study, a description of the methods used and details of the results obtained) (if available).

4. Information about the toxicity of capreomycin with respect to its composition (if available).

**Manufacturers of capreomycin powder for injection:**

1. A sample of each authorized capreomycin powder for injection (10 vials each of 1 g for each product belonging to the same batch, together with the corresponding certificate(s) of analysis) and a copy of the packaging indicating the labelled strength of the products.

2. A compilation of the specifications of the product together with a description of the methods used to determine them. For the methods to determine the content/strength and composition of the product the reference substance(s) used, the name(s) of the authorizing...
organization(s) and the declared strength(s) or assigned content(s) shall be indicated. In case chromatographic methods are used sample chromatograms shall also be submitted.

3. The outcome of investigations to correlate the total microbiological activity of capreomycin/capreomycin sulfate (or the activity of the components) with the mass concentration of the components (including information about the design of the performed study, a description of the methods used and details of the results obtained) (if available).

4. Information about the toxicity of capreomycin with respect to its composition (if available).

**Comparison of national capreomycin reference substances**

Not only assay methods based on different principles, also the lack of an international primary reference substance defining the activity of capreomycin may have affected the comparability of capreomycin dose regimes over time. To obtain relevant evidence, WHO shall organize laboratory investigations to determine:

1. the antimicrobiological activity of a common sample, capreomycin sulfate International Chemical Reference Substances (ICRS)³, according to the current provisions in the CP, IP and USP; and

2. the percentage mass concentrations of capreomycin IA, IB, IIA and IIB of the national reference substances prescribed by CP, IP and USP and analysed using the HPLC method described in the monograph on Capreomycin sulfate of The International Pharmacopoeia.

Based on the results of this survey, WHO shall evaluate jointly with i.a. the concerned pharmacopoeias the need to re-establish capreomycin ISA. The results will also help to further elucidate how the composition of capreomycin determines its activity.

**Bridging study to link the mass with the activity of capreomycin**

Considering the results of the landscape analysis of capreomycin APIs and products and on the comparison of national capreomycin reference substances, pharmacopoeias (in particular the CP, IP, USP and The International Pharmacopoeia) may decide to finish the transition from microbiological to a physicochemical assay for the capreomycin content by performing a bridging study to link the mass with the activity of the substance. Such a linkage would allow manufacturers to retain the current labelling of their products (i.e. the strength labelled in activity) and to seek regulatory approval to use a chromatographic method for the testing of their products.

A USP guidance document⁴ provides points to consider for the development of chromatographic or other physicochemical methods to replace microbiological assays. As a

³ Capreomycin sulfate ICRS is proposed as a common test sample because the chemical composition of the substance was thoroughly investigated during its establishment as a reference substances for physico-chemical tests according to The International Pharmacopoeia. The available analytical data, together with the results of the antimicrobiological determination may help to understand and to establish the correlation between the composition of capreomycin and its activity. Capreomycin ICRS is also needed as a reference substances for the determination under (2).

⁴ USP 39, chapter 1223, Validation of alternative methods to antibiotic microbial assays.
pivotal step, the process would involve the separation and purification of each antimicrobial moiety, process impurity and degradation product of the antibiotic and a subsequent determination of their individual, relative microbial activity.

To determine these relative microbial activities an international (primary) reference substance, capreomycin ISA, which defines the activity of capreomycin sulfate, would have to be re-established.

The alternative chromatographic method should be composition- and stability-indicating and would have to consider the specific absorptivity of the different components (in case the absorptivities differ significantly). The already published HPLC method in *The International Pharmacopoeia* is proposed to be used for this purpose.

**International harmonization of pharmacopoeial requirements for capreomycin**

The joint bridging study and its results shall also foster harmonization of pharmacopoeial requirements for capreomycin API and products. With the knowledge of the correlation between the composition and activity of capreomycin other pharmacopoeias, in particular CP, IP and USP, may consider to also switch to the alternative chromatographic method published in *The International Pharmacopoeia*.

In addition, the gained insights may facilitate future transitions from microbiological to physicochemical assays in monographs of other multicomponent antibiotics.

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**Proposed revision of the monograph on**

**Atenolol**

*(Atenololum)*

This is a draft revision of a monograph for *The International Pharmacopoeia* (Working document QAS/17.700, May 2017). It is proposed to revise the monograph based on information found in the European Pharmacopoeia and in the scientific literature.

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). In the online document changes from the current monograph are indicated in the text by *insert* or delete.

\[
\text{C}_{14}\text{H}_{22}\text{N}_{2}\text{O}_3
\]

**Relative molecular mass.** 266.3

**Chemical name.** 2-[[p-[[2-Hydroxy-3-(isopropylamino)propoxy]phenyl]acetamide (racemate); CAS Reg. No. 29122-68-7.

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

**Solubility.** Sparingly soluble in water; soluble in ethanol (≈750 g/L) TS; slightly soluble in dichloromethane R.

**Category.** Cardiovascular agent; β-adrenoreceptor blocking agent.

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

**Requirements**

Atenolol contains not less than 99.0% and not more than 101.0% of C\textsubscript{14}H\textsubscript{22}N\textsubscript{2}O\textsubscript{3}, calculated with reference to the dried substance.

**Identity tests**

- Either test A 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 atenolol RS or with the [reference spectrum](#) of atenolol.
B. The absorption spectrum of a 0.10 mg/mL solution in methanol R, when observed between 230 nm and 350 nm, exhibits 2 maxima at about 275 nm and 282 nm. The ratio of the absorbance at 275 nm to that at 282 nm is between 1.15 and 1.20.

C. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R4 as the coating substance and a mixture of 99 volumes of methanol R and 1 volume of ammonia (~260 g/L) TS as the mobile phase. Apply separately to the plate 10 μL of each of 2 solutions in methanol R containing (A) 10 mg of the test substance per mL and (B) 10 mg of atenolol RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air and examine the chromatogram in ultraviolet light (254 nm).

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

**Solution S.** Dissolve 0.10 g of the test substance in carbon-dioxide-free water R and dilute to 10.0 mL with the same solvent.

**Optical rotation (1.4).** Use solution S; α = +0.10 to –0.10.

**Clarity and colour of solution.** Solution (S) is clear and not more intensely coloured than degree 6 of the range of reference solutions of the most appropriate colour, when compared 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 section 1.11.2 Degree of coloration of liquids.]

**Chlorides.** Dissolve 0.25 g in a mixture of 2 mL of nitric acid (~130 g/L) TS and 20 mL of water and proceed as described under 2.2.1 Limit test for chlorides; the chloride content is not more than 1.0 mg/g.

**Sulfated ash (2.3).** Not more than 1.0 mg/g, determined using 1.0 g.

**Loss on drying.** Dry 1.0 g of the test substance to constant mass at 105°C; it loses not more than 5.0 mg/g.

**Related substances.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (12.5 cm × 4.0 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm). Prepare the following solution to be used as the mobile phase: dissolve 1.0 g of sodium octanesulfonate R and 0.4 g of tetrabutylammonium hydrogen sulfate R in 1000 mL of a mixture of 80 volumes of a 3.4 mg/mL solution of potassium dihydrogen phosphate R, the pH of the solution adjusted to 3.0 with phosphoric acid (~1440 g/L), 18 volumes of methanol R and 2 volumes of tetrahydrofuran R.

Prepare the following solutions in mobile phase. For solution (1) dissolve 50 mg of the test substance in 20 mL and dilute to 25.0 mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 1.0 mL of this solution to 10.0 mL. For solution (3) dissolve 2 mg of atenolol for system suitability RS (containing atenolol and the impurities B, F, G, I and J) in 1.0 mL of the mobile phase.

Operate with a flow rate of 0.6 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 226 nm.
Inject 10 μL of solution (3). Record the chromatograms for about 5 times the retention time of atenolol (retention time about 8 minutes). Use the chromatogram obtained with solution (3) and the chromatogram supplied with atenolol for system suitability RS to identify the peaks due to atenolol and the impurities B, F, G, I and J.

The test is not valid unless the resolution between the peaks due to the impurities J and I is at least 1.4.

Inject alternately 10 μL each of solutions (1) and (2).

In the chromatogram obtained with solution (1):
- the area of any peak corresponding to impurity B is not greater than 2 times the area of the peak due to atenolol in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to either impurity F, G, I or J is not greater than 1.5 times the area of the peak due to atenolol in the chromatogram obtained with solution (2) (0.15%);
- the area of any other impurity peak is not greater than the area of the peak due to atenolol in the chromatogram obtained with solution (2) (0.10%);
- the sum of the areas of all impurity peaks is not greater than 5 times the area of the peak due to atenolol in the chromatogram obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.5 times the area of the peak due to atenolol in the chromatogram obtained with solution (2) (0.05%).

**Assay.** Dissolve about 0.200 g, accurately weighed, in 80 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, determining the end-point potentiometrically.

Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 26.63 mg of C₁₄H₂₂N₂O₃.

**Impurities**

A. 2-(4-hydroxyphenyl)acetamide

B. 2-[4-[(2RS)-2,3-dihydroxypropoxy]phenyl]acetamide

D. 2-[4-[(2RS)-3-chloro-2-hydroxypropoxy]phenyl]acetamide
E. 2,2'-[(2-hydroxypropane-1,3-diyl)bis(oxy-4,1-phenylene)]diacetamide

F. 2,2'-[[[(propan-2-yl)azanediyl]bis[(2-hydroxypropane-3,1-diyl)oxy-4,1-phenylene]]
diacetamide


I. 2-[4-[(2RS)-3-(ethylamino)-2-hydroxypropoxy]phenyl]acetamide

J. 2-[4-[(2RS)-3-amino-2-hydroxypropoxy]phenyl]acetamide

***
1.15.1

Capillary electrophoresis

This is a draft proposed text for The International Pharmacopoeia (Working document QAS/16.698, May 2017). This text is based on the internationally harmonized texts developed by the Pharmacopoeial Discussion Group (PDG). It has been developed in line with the style and requirements used in The International Pharmacopoeia. The permission to reproduce the text will be requested when the text is adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects.

This text is based on the internationally harmonized texts developed by the Pharmacopoeial Discussion Group (PDG). It has been developed in line with the style and requirements used in The International Pharmacopoeia.

General principles

Capillary electrophoresis is a physical method of analysis based on the migration, inside a capillary, of charged analytes dissolved in an electrolyte solution under the influence of a direct-current electric field.

The migration velocity of the analyte under an electric field of intensity E is determined by the electrophoretic mobility of the analyte and the electroosmotic mobility of the buffer inside the capillary. The electrophoretic mobility of a solute (\(\mu_{ep}\)) depends on the characteristics of the solute (electrical charge, molecular size and shape) and the characteristics of the buffer in which the migration takes place (type and ionic strength of the electrolyte, pH, viscosity and additives). The electrophoretic velocity (\(v_{ep}\)) of a solute, assuming a spherical shape, is as follows:

\[
v_{ep} = \mu_{ep} \times E = \left(\frac{q}{6\pi\eta r}\right) \times \left(\frac{V}{L}\right)
\]

in which \(q\) is the effective charge of the solute; \(\eta\) is the viscosity of the electrolyte solution; \(r\) is the Stoke's radius of the solute; \(V\) is the applied voltage; and \(L\) is the total length of the capillary.

When an electric field is applied through the capillary filled with buffer, a flow of solvent, called electroosmotic flow, is generated inside the capillary. Its velocity depends on the electroosmotic mobility (\(\mu_{eo}\)), which in turn depends on the charge density on the capillary internal wall and the buffer characteristics. The electroosmotic velocity (\(v_{eo}\)) is given by the equation:

\[
v_{eo} = \mu_{eo} \times E = \left(\frac{\varepsilon \zeta}{\eta}\right) \times \left(\frac{V}{L}\right)
\]

in which \(\varepsilon\) is the dielectric constant of the buffer; \(\zeta\) is the zeta potential of the capillary surface; and the other terms are as defined above.
The velocity of the solute (\(v\)) is given by the equation:

\[ v = v_{ep} + v_{eo} \]

The electrophoretic mobility of the analyte and the electroosmotic mobility may act in the same direction or in opposite directions, depending on the charge of the solute. In normal capillary electrophoresis, anions will migrate in the opposite direction to the electroosmotic flow and their velocities will be smaller than the electroosmotic velocity. Cations will migrate in the same direction as the electroosmotic flow and their velocities will be greater than the electroosmotic velocity. Under conditions in which there is a fast electroosmotic velocity with respect to the electrophoretic velocity of the solutes, both cations and anions can be separated in the same run.

The time (\(t\)) taken by the solute to migrate the distance (\(l\)) from the injection end of the capillary to the detection point (capillary effective length) is as follows:

\[ t = \frac{l}{v_{ep} + v_{eo} = \frac{l(L)}{(\mu_{ep} + \mu_{eo}) \times V}} \]

in which the other terms are as defined above.

In general, uncoated fused-silica capillaries above pH 3 have negative charge due to ionized silanol groups in the inner wall. Consequently, the electroosmotic flow is from anode to cathode. The electroosmotic flow must remain constant from run to run to obtain good reproducibility in the migration velocity of the solutes. For some applications, it might be necessary to reduce or suppress the electroosmotic flow by modifying the inner wall of the capillary or by changing the concentration, composition and/or the pH of the buffer solution.

After the introduction of the sample into the capillary each analyte ion of the sample migrates within the background electrolyte as an independent zone according to its electrophoretic mobility. Zone dispersion, that is the spreading of each solute band, results from different phenomena. Under ideal conditions, the sole contribution to the solute-zone broadening is molecular diffusion of the solute along the capillary (longitudinal diffusion). In this ideal case, the efficiency of the zone, expressed as the number of theoretical plates (\(N\)), is given by:

\[ N = \frac{(\mu_{ep} + \mu_{eo}) \times V \times l}{2 \times D \times L} \]

in which \(D\) is the molecular diffusion coefficient of the solute in the buffer.

In practice, other phenomena, such as heat dissipation, sample adsorption onto the capillary wall, mismatched conductivity between sample and buffer, length of the injection plug, detector cell size and unlevelled buffer reservoirs, can also significantly contribute to band dispersion. Separation between two bands (expressed by the resolution \(R_s\)) can be obtained by modification of the electrophoretic mobility of the analytes, by the electroosmotic mobility induced in the capillary and by increasing the efficiency for the band of each analyte as follows:

\[ R_s = \frac{\sqrt{N(\mu_{epb} - \mu_{epa})}}{4(\mu_{ep} + \mu_{eo})} \]

in which \(\mu_{epa}\) and \(\mu_{epb}\) are the electrophoretic mobilities of the two analytes to be separated; is the average electrophoretic mobility of the two analytes calculated as:

\[ \overline{\mu_{ep}} = \frac{1}{2}(\mu_{epb} + \mu_{epa}) \]
Apparatus
An apparatus for capillary electrophoresis is composed of a high voltage controllable direct current power supply; two buffer reservoirs held at the same level and containing specified anodic and cathodic solutions; two electrode assemblies (cathode and anode) immersed in the buffer reservoirs and connected to the power supply; a separation capillary usually made of fused-silica, sometimes with an optical viewing window aligned with the detector, depending on the detector type, with the ends of the capillary placed in the buffer reservoirs and the capillary being filled with a solution specified in a given monograph; a suitable injection system; a detector capable of monitoring the amount of substance of interest passing through a segment of the separation capillary at a given time, generally based on absorption spectrophotometry (ultraviolet (UV) and visible), fluorimetry, conductimetric, amperometric, or mass spectrometric detection, depending on the specific applications, or even indirect detection to detect non-UV-absorbing and nonfluorescent compounds; a thermostatic system capable of maintaining a constant temperature inside the capillary, recommended to obtain good separation reproducibility; a recorder; and a suitable integrator or a computer.

The definition of the injection process and its automation are critical for precise quantitative analysis. Modes of injection include gravity, pressure or vacuum, or electrokinetic injection. The amount of each sample component introduced electrokinetically depends on its electrophoretic mobility, leading to possible discrimination using this injection mode.

It is expected that the capillary, the buffer solutions, the preconditioning method, the sample solution, and the migration conditions will be specified in the individual monograph. The electrolytic solution employed is filtered to remove particles and degassed to avoid bubble formation that could interfere with the detection system or interrupt the electrical contact in the capillary during the separation run. To achieve reproducible migration time of the solutes, it would be necessary to develop, for each analytical method, a rigorous rinsing routine.

Capillary zone electrophoresis

Principle
In capillary zone electrophoresis, analytes are separated in a capillary containing only buffer without any anticonvective medium. In this technique, separation takes place because the different components of the sample migrate as discrete bands with different velocities. The velocity of each band depends on the electrophoretic mobility of the solute and the electroosmotic flow on the capillary (see “General principles”). Coated capillaries can be used to increase the separation capacity of those substances adsorbing on fused-silica surfaces.

This mode of capillary electrophoresis is appropriate for the analysis of small (molecular weight < 2000) and large (2000 < MW < 100,000) molecules. Due to the high efficiency achieved in capillary zone electrophoresis, separation of molecules having only minute differences in their charge-to-mass ratio can be effected. This separation mode also allows the separation of chiral compounds by addition of chiral selectors to the separation buffer.
**Optimization**

Optimization of the separation is a complex process where several separation parameters can play a major role. The main factors to be considered in the development of the separations are instrumental and electrolytic solution parameters.

**Instrumental parameters**

**Voltage.** A Joule heating plot is useful in optimizing the applied voltage and column temperature. The separation time is inversely proportional to applied voltage. However, an increase in the voltage used can cause excessive heat production, giving rise to temperature and, as a result, viscosity gradients in the buffer inside the capillary, which causes band broadening and decreases resolution.

**Polarity.** Electrode polarity can be normal (anode at the inlet and cathode at the outlet) and the electroosmotic flow will move toward the cathode. If the electrode polarity is reversed the electroosmotic flow is away from the outlet and only charged analytes with electroosmotic mobilities greater than the electroosmotic flow will pass to the outlet.

**Temperature.** The main effect of temperature is observed on buffer viscosity and electrical conductivity, thus affecting migration velocity. In some cases, an increase in capillary temperature can cause a conformational change of some proteins, modifying their migration time and the efficiency of the separation.

**Capillary.** The length and internal diameter of the capillary affects the analysis time, the efficiency of separations and the load capacity. Increasing both effective length and total length can decrease the electric fields, at a constant voltage, which increases migration time. For a given buffer and electric field, heat dissipation (thus, sample band broadening) depends on the internal diameter of the capillary. The latter also affects the detection limit, depending on the sample volume injected into the capillary and the detection system used.

The adsorption of sample components on the capillary wall limits efficiency; therefore, methods to avoid these interactions should be considered in the development of a separation method. In the specific case of proteins, several strategies have been devised to avoid adsorption on the capillary wall. Some of these strategies (use of extreme pH and adsorption of positively charged buffer additives) only require modification of the buffer composition to prevent protein adsorption. Other strategies include the coating of the internal wall of the capillary with a polymer covalently bonded to the silica that prevents interaction between the proteins and the negatively charged silica surface. For this purpose, ready-to-use capillaries with coatings consisting of neutral-hydrophilic, cationic and anionic polymers are commercially available.

**Electrolytic solution parameters**

**Buffer type and concentrations.** Suitable buffers for capillary electrophoresis have an appropriate buffer capacity in the pH range of choice and low mobility to minimize current generation.

To minimize band distortion, it is important to match buffer-ion mobility to solute mobility whenever possible. The type of sample solvent used is important to achieve on-column sample focusing, which increases separation efficiency and improves detection. Also, an increase in buffer concentration at a given pH decreases electroosmotic flow and solute velocity.
**Buffer pH.** The pH of the buffer can affect separation by modifying the charge of the analyte or additives and by changing the electroosmotic flow. For protein and peptide separation, a change in the pH of the buffer from above the isoelectric point (pI) to below the pI changes the net charge of the solute from negative to positive. An increase in the buffer pH generally increases the electroosmotic flow.

**Organic solvents.** Organic modifiers, such as methanol, acetonitrile and others may be added to the aqueous buffer to increase the solubility of the solute or other additives and/or to affect the ionization degree of the sample components. The addition of these organic modifiers to the buffer generally causes a decrease in the electroosmotic flow.

**Additives for chiral separations.** To separate optical isomers, a chiral selector is added to the separation buffer. The most commonly used chiral selectors are cyclodextrins, although in some cases crown ethers, certain polysaccharides or even proteins can be used. Because chiral recognition is governed by the different interactions between the chiral selector and each of the enantiomers the resolution achieved for the chiral compounds depends largely on the type of chiral selector used.

While developing a given separation it may be useful to test cyclodextrins having a different cavity size (α-, β-, or γ-cyclodextrin) or modified cyclodextrins with neutral (methyl, ethyl, hydroxyalkyl, etc.) or ionizable (aminomethyl, carboxymethyl, sulfobutylether, etc.) moieties. When using modified cyclodextrins, batch-to-batch variations in the degree of substitution of the cyclodextrins must be taken into account because it will influence the selectivity. The resolution of chiral separations is also controlled by the concentration of the chiral selector, the composition and pH of the buffer and the separation temperature. Organic additives, such as methanol or urea, can also affect the resolution of separation.

**Capillary gel electrophoresis**

In capillary gel electrophoresis, separation takes place inside a capillary filled with a gel that acts as a molecular sieve. Molecules with similar charge-to-mass ratios are separated according to molecular size because smaller molecules move more freely through the network of the gel and therefore migrate faster than larger molecules. Different biological macromolecules (for example, proteins and DNA fragments), which often have similar charge-to-mass ratios, can thus be separated according to their molecular mass by capillary gel electrophoresis.

**Characteristics of gels**

Two types of gels are used in capillary electrophoresis: permanently coated gels and dynamically coated gels. Permanently coated gels are prepared inside the capillary by polymerization of monomers. One example of such a gel is a cross-linked polyacrylamide. This type of gel is usually bonded to the fused-silica wall and cannot be removed without destroying the capillary. For protein analysis under reducing conditions the separation buffer usually contains sodium dodecyl sulfate and the sample is denatured by heating in a mixture of sodium dodecyl sulfate and 2-mercaptoethanol or dithiothreitol before injection. When non-reducing conditions are used (for example, analysis of an intact antibody), 2-mercaptoethanol and dithiothreitol are not used. Optimization of separation in a cross-linked gel is obtained by modifying the separation buffer (see “Capillary zone electrophoresis”) and by controlling the gel porosity during the gel preparation. For cross-linked polyacrylamide gels the porosity can
be modified by changing the concentration of acrylamide and/or the ratio of the cross-linker. As a rule, a decrease in the porosity of the gel leads to a decrease in the mobility of the solutes. Due to the rigidity of this type of gel, only electrokinetic injection can be used.

Dynamically coated gels are hydrophilic polymers (i.e. linear polyacrylamide, cellulose derivatives, dextran, etc.) which can be dissolved in aqueous separation buffers, giving rise to a separation medium that also acts as a molecular sieve. These polymeric separation media are easier to prepare than cross-linked polymers. They can be prepared in a vial and filled by pressure in a wall-coated capillary with no electroosmotic flow. Replacing the gel before every injection generally improves the separation reproducibility. The porosity of the dynamically coated gels can be increased by using polymers of higher molecular mass (at a given polymer concentration) or by decreasing the polymer concentration (for a given polymer molecular mass). A decrease in gel porosity leads to a decrease in the mobility of the solute for the same buffer. Both hydrodynamic and electrokinetic injection techniques can be used because the dissolution of these polymers in the buffer gives low viscosity solutions.

**Capillary isoelectric focusing**

**Principle**

In isoelectric focusing the molecules migrate under the influence of the electric field, so long as they are charged, in a pH gradient generated by ampholytes having pI values in a wide range (polyaminocarboxylic acids), dissolved in the separation buffer.

The three basic steps in capillary isoelectric focusing are loading, focusing and mobilization.

**Loading step.** Two methods may be employed.

Loading in one step: The sample is mixed with ampholytes and introduced into the capillary by pressure or vacuum.

Sequential loading: A leading buffer, then the ampholytes, then the sample mixed with ampholytes, again ampholytes alone, and finally the terminating buffer are introduced into the capillary. The volume of the sample must be small enough so as not to modify the pH gradient.

**Focusing step.** When the voltage is applied, ampholytes migrate toward the cathode or the anode according to their net charge, creating the pH gradient from anode (lower pH) to cathode (higher pH). During this step the components to be separated migrate until they reach a pH corresponding to their isoelectric point, and the current drops to very low values.

**Mobilization step.** If mobilization is required for detection, use one of the following three methods.

Method 1: Mobilization is accomplished during the focusing step, under the influence of the electroosmotic flow when this flow is small enough to allow the focusing of the components.

Method 2: Mobilization is accomplished by application of positive pressure after the focusing step.

Method 3: Mobilization is achieved after the focusing step by adding salts to the cathode reservoir or the anode reservoir, depending on the direction chosen for mobilization, in order to alter the pH in the capillary when the voltage is applied.
As the pH is changed the proteins and ampholytes are mobilized in the direction of the reservoir, which contains added salts and pass the detector.

The separation achieved is expressed as $\Delta pI$ and depends on the pH gradient ($dpH/dx$), the number of ampholytes having different $pI$ values, the molecular diffusion coefficient ($D$), the intensity of the electric field ($E$) and the variation of the electrophoretic mobility of the analyte with the pH ($-d\mu/dpH$):

$$\Delta pI = 3 \times \sqrt{\frac{D(dpH/dx)}{E(-d\mu/dpH)}}$$

**Optimization**

The major parameters that need to be considered in the development of separations are the following:

**Voltage.** The use of high fields from 300 V/cm to 1000 V/cm during the focusing step.

**Capillary.** The electroosmotic flow must be reduced or suppressed depending on the mobilization strategy selected (see above). Coated capillaries tend to reduce the electroosmotic flow.

**Solutions.** The anode buffer reservoir is filled with a solution of a lower pH than the $pI$ of the most acidic ampholyte, and the cathode reservoir is filled with a solution with a higher pH than the $pI$ of the most basic ampholyte. Phosphoric acid for the anode and sodium hydroxide for the cathode are frequently used.

Addition of a polymer, like methylcellulose, in the ampholyte solution tends to suppress convective forces (if any) and electroosmotic flow by increasing the viscosity. Commercial ampholytes covering many pH ranges are available and may also be mixed to obtain an expanded pH range. Broad pH ranges are used to estimate the $pI$, whereas narrower ranges are employed to improve accuracy. Calibration can be made by correlating migration time with the $pI$ of a series of standard protein markers. During the focusing step, precipitation of proteins at their $pI$ can be prevented, if necessary, using buffer additives such as glycerol, surfactants, urea, or zwitterionic buffers. However, depending on the concentration, urea can denature proteins.

**Micellar electrokinetic chromatography**

**Principle**

Separation takes place in an electrolytic solution that contains a surfactant at a concentration above the critical micellar concentration (CMC). The solute molecules are distributed between the aqueous buffer and the pseudostationary phase composed by the micelles according to the solute’s partition coefficient. The technique can be considered as a hybrid of electrophoresis and chromatography. It is a technique that can be used for the separation of both neutral and charged solutes maintaining the efficiency, speed and instrumental suitability of capillary electrophoresis. One of the most widely used surfactants in micellar electrokinetic chromatography (MEKC) is the anionic surfactant, sodium dodecyl sulfate, although other surfactants, such as cationic surfactant cetyl trimethyl ammonium salts, have also been used.
The separation mechanism is as follows. At neutral and alkaline pH, a strong electroosmotic flow is generated and moves the separation buffer ions in the direction of the cathode. If sodium dodecyl sulfate is used as surfactant the electrophoretic migration of the anionic micelle is in the opposite direction, towards the anode. As a result, the overall micelle migration velocity is slowed compared to the bulk flow of the electrolytic solution. In the case of neutral solutes, because the analyte can partition between the micelle and the aqueous buffer and has no electrophoretic mobility, the analyte migration velocity will depend only on the partition coefficient between the micelle and the aqueous buffer. In the electropherogram the peaks corresponding to each uncharged solute are always between that of the electroosmotic flow marker and that of the micelle; and the time elapsed between these two peaks is called the separation window. For electrically charged solutes the migration velocity depends on both the partition coefficient of the solute between the micelle and the aqueous buffer and on the electrophoretic mobility of the solute in the absence of micelles.

Since the mechanism in MEKC of neutral and weakly ionized solutes is essentially chromatographic, migration of the solute and resolution can be rationalized in terms of the retention factor of the solute ($k'$), also referred to as mass distribution ratio ($D_m$), which is the ratio between the number of moles of solute in the micelle to those in the mobile phase. For a neutral compound, $k'$ is given as follows:

$$ k' = \frac{t_r - t_0}{t_0 \times \left(1 - \frac{t_r}{t_{mc}}\right)} = K \times \frac{V_s}{V_M} $$

in which $t_r$ is the migration time of the solute; $t_0$ is the analysis time of the unretained solute obtained by injecting an electroosmotic flow marker that does not enter the micelle (e.g. methanol); $t_{mc}$ is the micelle migration time measured by injecting a micelle marker, such as Sudan III, which migrates continuously associated in the micelle; $K$ is the partition coefficient of the solute; $V_s$ is the volume of the micellar phase; and $V_M$ is the volume of the mobile phase.

The resolution between two closely-migrating solutes ($R_s$) is as follows:

$$ R_s = \frac{\sqrt{N}}{4} \times \frac{\alpha - 1}{\alpha} \times \frac{k_b'}{k_a' + 1} \times \frac{1 - \left(\frac{t_0}{t_{mc}}\right)}{1 + k_a' \times \left(\frac{t_0}{t_{mc}}\right)} $$

in which $N$ is the number of theoretical plates for one of the solutes; $\alpha$ is the selectivity; and $k_a'$ and $k_b'$ are retention factors for both solutes, respectively ($k_b' > k_a'$).

Similar, but not identical, equations give $k'$ and $R_s$ values for electrically charged solutes.

**Optimization**

The main parameters to be considered in the development of separations by MEKC are instrumental and electrolytic solution parameters.

**Instrumental parameters**

**Voltage.** Separation time is inversely proportional to applied voltage. However, an increase in voltage can cause excessive heat production that gives rise to temperature gradients and viscosity gradients of the buffer in the cross section of the capillary. This effect can be significant with high conductivity buffers, such as those containing micelles. Poor heat dissipation causes band broadening and decreases resolution.
Temperature. Variations in capillary temperature affect the partition coefficient of the solute between the buffer and the micelles, the critical micellar concentration and the viscosity of the buffer. These parameters contribute to the migration time of the solutes. The use of a good cooling system improves the reproducibility of the migration time for the solutes.

Capillary. As in capillary zone electrophoresis, length and internal diameter of the capillary contribute to analysis time and efficiency of separations. Increasing both effective length and total length can decrease the electrical fields, working at constant voltage, and will increase migration time and improve the separation efficiency. The internal diameter controls heat dissipation, for a given buffer and electrical field, and consequently broadening of the sample band.

Electrolytic solution parameters
Surfactant type and concentration. The type of surfactant, as the stationary phase in chromatography, affects the resolution because it modifies separation selectively. The log $k'$ of a neutral compound increases linearly with the concentration of surfactant in the mobile phase. When $k'$ approaches the value of

$$\sqrt{t_{mc}} / t_0$$

resolution in MEKC reaches a maximum. Modifying the concentration of surfactant in the mobile phase changes the resolution.

Buffer pH. pH does not modify the partition coefficient of non-ionized solutes, but it can modify the electroosmotic flow in uncoated capillaries. A decrease in the buffer pH decreases the electroosmotic flow and, therefore, increases the resolution of the neutral solutes in MEKC, resulting in a longer analysis time.

Organic solvents. To improve MEKC separation of hydrophobic compounds, organic modifiers (methanol, propanol, acetonitrile, etc.) can be added to the electrolytic solution. The addition of these modifiers generally decreases migration time and selectivity of the separation. The addition of organic modifiers affects critical micellar concentration; thus, a given surfactant concentration can be used only with a certain percentage of organic modifier before the micellization is inhibited or adversely affected, resulting in the absence of micelles and, therefore, the absence of the partition. The dissociation of micelles in the presence of a high content of organic solvent does not always mean that the separation will no longer be possible, because in some cases, the hydrophobic interaction between the ionic surfactant monomer and the neutral solutes forms solvophobic complexes that can be separated electrophoretically.

Additives for chiral separations. For the separation of enantiomers using MEKC a chiral selector is included in the micellar system, either covalently bound to the surfactant or added to the micellar separation electrolyte. Micelles that have a moiety with chiral discrimination properties include salts, $N$-dodecanoyl-l-amino acids, bile salts, etc. Chiral resolution can also be achieved using chiral discriminators, such as cyclodextrins, added to the electrolytic solutions that contain micellized achiral surfactants.
**Other additives.** Selectivity can be modified by adding chemicals to the buffer. Addition of several types of cyclodextrins to the buffer is also used to reduce the interaction of hydrophobic solutes with the micelle, increasing the selectivity for this type of compound. The addition of substances able to modify solute-micelle interactions by adsorption on the latter has been used to improve the selectivity of the separations in MEKC. These additives may consist of a second surfactant (ionic or nonionic), which gives rise to mixed micelles or metallic cations that dissolve in the micelle and form coordination complexes with the solutes.

**Quantification**

Peak areas must be divided by the corresponding migration time to give the corrected area in order to compensate for the shift in migration time from run to run, thus reducing the variation of the response. Dividing the peak areas by migration time will also compensate for the different responses of sample constituents with different migration times. Where an internal standard is used, check that no peak of the substance to be examined is masked by that of the internal standard.

**Calculations**

From the values obtained, calculate the content of a component or components being determined. When indicated, the percentage of one (or more) components of the sample to be examined is calculated by determining the corrected area(s) of the peak(s) as a percentage of the total of the corrected areas of all the peaks, excluding those due to solvents or any added reagents (normalization procedure). The use of an automatic integration system (integrator or data acquisition and processing system) is recommended.

**System suitability**

In order to check the behaviour of the capillary electrophoresis system, system suitability parameters are used. The choice of these parameters depends on the mode of capillary electrophoresis used. The parameters include the following: retention factor\( k' \) (used only for micellar electrokinetic chromatography), apparent number of theoretical plates (\( N \)), the symmetry factor (\( A_s \)), and the resolution (\( R_s \)). In previous sections the theoretical expressions for \( N \) and \( R_s \) have been described but more practical equations that allow for the determination of these suitability parameters using the electropherograms are given below.

**Apparent number of theoretical plates**

The apparent number of \( N \) may be calculated from the formula:

\[
N = 5.54 \left( \frac{t_R}{w_h} \right)^2
\]

in which \( t_R \) is the migration time or distance along the baseline between the point of injection and the perpendicular dropped from the maximum of the peak corresponding to the component; and \( w_h \) is the peak width at half-height.
Resolution

The Rs between peaks of similar heights of two components may be calculated from the formula:

\[ R_s = 1.18 \left( \frac{t_{R2} - t_{R1}}{w_{h1} + w_{h2}} \right) \]

where \( t_{R1} \) and \( t_{R2} \) are the migration times or distances along the baseline between the point of injection and the perpendiculars dropped from the maxima of two adjacent peaks; and \( w_{h1} \) and \( w_{h2} \) are the peak widths at half-height.

When appropriate, the Rs may also be calculated by measuring the height of the valley (\( H_v \)) between two partly resolved peaks in a standard preparation, the height of the smaller peak (\( H_p \)), and calculating the peak-to-valley ratio:

\[ p/v = \frac{H_p}{H_v} \]

Symmetry factor

The symmetry factor of As may be calculated using the formula:

\[ A_s = \frac{w_{0.05}}{2d} \]

where \( w_{0.05} \) is the width of the peak at one-twentieth of the peak height; and \( d \) is the distance between the perpendicular dropped from the peak maximum and the leading edge of the peak at one-twentieth of the peak height.

Other suitability parameters include tests for area repeatability (standard deviation of areas or of area/migration time) and tests for migration time repeatability (standard deviation of migration time). Migration time repeatability provides a test for the suitability of the capillary washing procedures. An alternative practice to avoid the lack of repeatability of the migration time is to use a migration time relative to an internal standard.

Signal-to-noise ratio

A test for the verification of the signal-to-noise ratio for a standard preparation or the determination of the limit of quantification may also be useful for the determination of related substances. The detection limit and quantification limit correspond to a signal-to-noise ratio of 3 and 10, respectively. The signal-to-noise ratio (\( S/N \)) is calculated as follows:

\[ S/N = \frac{2H}{h} \]

where \( H \) is the height of the peak corresponding to the component concerned in the electropherogram obtained with the specified reference solution, measured from the maximum of the peak to the extrapolated baseline of the signal observed over a distance equal to twenty times the width at half-height; and \( h \) is the range of the background in an electropherogram obtained after injection of a blank, observed over a distance equal to twenty times the width at the half-height of the peak in the electropherogram obtained with the prescribed reference solution and, if possible, situated equally around the place where this peak would be found.

***
The following medicines quality-related guidelines have been posted for public comment on the WHO website. The respective working documents with line numbers are 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).

- **Good practices for desk assessment**
  
  *Guidance on good practices for desk assessment for compliance with good manufacturing practices, good laboratory practices and good clinical practices for marketing authorization of medical products*
  
  **Working document QAS/17.713 (May 2017)**
  
  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.

- **Considerations for requesting analysis of medicines samples**
  

- **Model certificate of analysis**
  
  
  These two documents are revisions of 2002 guidance texts. The proposed updates take into account new trends and international developments.

- **“SRA” collaborative procedure**
  
  *Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products approved by stringent regulatory authorities*
  
  **Working document QAS/17.704 (March 2017)**
  
  This text proposes scheme for national medicines regulatory authorities and pharmaceutical companies (manufacturers) to facilitate registrations of medicines approved by stringent regulatory authorities.

- **Good herbal processing practices**
  
  *Revised Draft: WHO guidelines on good herbal processing practices (GHPP) for herbal medicines*
  
  **WHO/SDS/TCM (March 2017)**
  
  This text proposes technical guidance on processing of herbs to produce herbal materials, of herbal materials to produce herbal preparations, and of herbal materials or herbal preparations to produce herbal dosage forms.
ATC/DDD classification

The Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) as a measuring unit are tools for exchanging and comparing data on drug use at international, national or local levels. The ATC/DDD system has become the gold standard for international drug utilization research. It is maintained by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway. Visit [www.whocc.no](http://www.whocc.no) for more information.

ATC/DDD classification (temporary)

The following ATC codes and DDDs were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in March 2017. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology before 1 September 2017. If no objections are received before this date, the new ATC codes and DDDs will be considered final and included in the January 2018 version of the ATC/DDD Index.

New ATC 5th level codes

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### Change of ATC level names

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### New DDDs

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* Administration Route: O = oral; P = parenteral.
1) DDD remains temporary for another period.

### Changes of DDDs

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* Administration Route: O = oral; P = parenteral.
ATC/DDD classification (final)

The following ATC codes, DDDs and alterations were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in October 2016. These are considered as final and will be included in the January 2018 version of the ATC/DDD Index.

### New ATC 5th level codes

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<td>Lavandulae aetheroleum</td>
<td>N05BX05</td>
</tr>
<tr>
<td>lutetium (177Lu) oxodotreotide</td>
<td>V10XX04</td>
</tr>
<tr>
<td>mepyramine theophyllinacetate</td>
<td>R03DA12</td>
</tr>
<tr>
<td>migalastat</td>
<td>A16AX14</td>
</tr>
<tr>
<td>netarsudil</td>
<td>S01EX05</td>
</tr>
<tr>
<td>niraparib</td>
<td>L01XX54</td>
</tr>
<tr>
<td>obiltoxaimab</td>
<td>J06BB22</td>
</tr>
<tr>
<td>olaratumab</td>
<td>L01XC27</td>
</tr>
<tr>
<td>opicapone</td>
<td>N04BX04</td>
</tr>
<tr>
<td>ozenoxacin</td>
<td>D06AX14</td>
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<tr>
<td>padeliporfin</td>
<td>L01XD07</td>
</tr>
<tr>
<td>pegteogrrastim</td>
<td>L03AA17</td>
</tr>
<tr>
<td>plitidepsin</td>
<td>L01XX57</td>
</tr>
<tr>
<td>ramipril, amlodipine and hydrochlorothiazide</td>
<td>C09BX03</td>
</tr>
<tr>
<td>rebamipide</td>
<td>A02BX14</td>
</tr>
<tr>
<td>ribociclib</td>
<td>L01XE42</td>
</tr>
<tr>
<td>romosozumab</td>
<td>M05BX06</td>
</tr>
<tr>
<td>rosuvastatin, amlodipine and perindopril</td>
<td>C10BX14</td>
</tr>
<tr>
<td>rosuvastatin, perindopril and indapamide</td>
<td>C10BX13</td>
</tr>
<tr>
<td>rucaparib</td>
<td>L01XX55</td>
</tr>
<tr>
<td>semaglutide</td>
<td>A10BJ06</td>
</tr>
<tr>
<td>sodium zirconium cyclosilicate</td>
<td>V03AE10</td>
</tr>
<tr>
<td>sofosbuvir and velpatasvir</td>
<td>J05AX69</td>
</tr>
<tr>
<td>suvorexant</td>
<td>N05CM19</td>
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</tbody>
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Continued
New ATC 5th level codes (continued)

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>tetracaine, combinations</td>
<td>N01BA53</td>
</tr>
<tr>
<td>velmanase alfa</td>
<td>A16AB15</td>
</tr>
<tr>
<td>zoster, purified antigen</td>
<td>J07BK03</td>
</tr>
</tbody>
</table>

1) The ATC code will be altered to J05AP55 in connection with the implementation of the new ATC 4th level J05AP Antivirals for treatment of HCV infections in 2018.

New ATC level codes (other than 5th levels)

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antivirals for treatment of HCV infections</td>
<td>J05AP</td>
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</table>

Change of ATC codes

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>Previous ATC</th>
<th>New ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>argipressin</td>
<td>H01BA06</td>
<td>H01BA01</td>
</tr>
<tr>
<td>asunaprevir</td>
<td>J05AE15</td>
<td>J05AP06</td>
</tr>
<tr>
<td>benzydamine</td>
<td>A01AD02</td>
<td>R02AX03</td>
</tr>
<tr>
<td>boceprevir</td>
<td>J05AE12</td>
<td>J05AP03</td>
</tr>
<tr>
<td>ceftriaxone, combinations</td>
<td>J01DD54</td>
<td>J01DD63</td>
</tr>
<tr>
<td>daclatasvir</td>
<td>J05AX14</td>
<td>J05AP07</td>
</tr>
<tr>
<td>dasabuvir</td>
<td>J05AX16</td>
<td>J05AP09</td>
</tr>
<tr>
<td>dasabuvir, ombitasvir, paritaprevir and ritonavir</td>
<td>J05AX66</td>
<td>J05AP52</td>
</tr>
<tr>
<td>elbasvir and grazoprevir</td>
<td>J05AX68</td>
<td>J05AP54</td>
</tr>
<tr>
<td>faldaprevir</td>
<td>J05AE13</td>
<td>J05AP04</td>
</tr>
<tr>
<td>ombitasvir, paritaprevir and ritonavir</td>
<td>J05AX67</td>
<td>J05AP53</td>
</tr>
<tr>
<td>ribavirin</td>
<td>J05AB04</td>
<td>J05AP01</td>
</tr>
<tr>
<td>simeprevir</td>
<td>J05AE14</td>
<td>J05AP05</td>
</tr>
<tr>
<td>sofosbuvir</td>
<td>J05AX15</td>
<td>J05AP08</td>
</tr>
<tr>
<td>sofosbuvir and ledipasvir</td>
<td>J05AX65</td>
<td>J05AP51</td>
</tr>
<tr>
<td>telaprevir</td>
<td>J05AE11</td>
<td>J05AP02</td>
</tr>
</tbody>
</table>

1) ATC level name altered to vasopressin (argipressin).
2) Split of code. Alteration of ATC code applies only for benzydamine lozenges.
3) Split of code. Combinations of ceftriaxone and other substances remain in J01DD54 while combinations of ceftriaxone and beta-lactamase inhibitors are moved to J01DD63.

Change of ATC level names

<table>
<thead>
<tr>
<th>Previous</th>
<th>New</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxicillin and enzyme inhibitor</td>
<td>amoxicillin and beta-lactamase inhibitor</td>
<td>J01CR02</td>
</tr>
<tr>
<td>ampicillin and enzyme inhibitor</td>
<td>ampicillin and beta-lactamase inhibitor</td>
<td>J01CR01</td>
</tr>
<tr>
<td>Bile acid preparations</td>
<td>Bile acids and derivatives</td>
<td>A05AA</td>
</tr>
<tr>
<td>cefoperazone, combinations</td>
<td>cefoperazone and beta-lactamase inhibitor</td>
<td>J01DD62</td>
</tr>
<tr>
<td>cefotaxime, combinations</td>
<td>cefotaxime and beta-lactamase inhibitor</td>
<td>J01DD51</td>
</tr>
</tbody>
</table>

Continued
### Change of ATC codes (continued)

<table>
<thead>
<tr>
<th>ATC level name / INN</th>
<th>Previous ATC</th>
<th>New ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ceftazidime, combinations</td>
<td>ceftazidime and beta-lactamase inhibitor</td>
<td>J01DD52</td>
</tr>
<tr>
<td>ceftolozane and enzyme inhibitor</td>
<td>ceftolozane and beta-lactamase inhibitor</td>
<td>J01DI54</td>
</tr>
<tr>
<td>imipenem and enzyme inhibitor</td>
<td>imipenem and cilastatin</td>
<td>J01DH51</td>
</tr>
<tr>
<td>piperacillin and enzyme inhibitor</td>
<td>piperacillin and beta-lactamase inhibitor</td>
<td>J01CR05</td>
</tr>
<tr>
<td>ticarcillin and enzyme inhibitor</td>
<td>ticarcillin and beta-lactamase inhibitor</td>
<td>J01CR03</td>
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</table>

### New DDDs

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>DDD</th>
<th>unit</th>
<th>Adm.R*</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td>rebamipide</td>
<td>0.3 g</td>
<td>O</td>
<td></td>
<td>A02BX14</td>
</tr>
<tr>
<td>voglibose</td>
<td>0.6 mg</td>
<td>O</td>
<td></td>
<td>A10BF03</td>
</tr>
<tr>
<td>migalastat</td>
<td>61.5 mg</td>
<td>O</td>
<td></td>
<td>A16AX14</td>
</tr>
<tr>
<td>vorapaxar</td>
<td>2.08 mg</td>
<td>O</td>
<td></td>
<td>B01AC26</td>
</tr>
<tr>
<td>selexipag</td>
<td>1.8 mg</td>
<td>O</td>
<td></td>
<td>B01AC27</td>
</tr>
<tr>
<td>ferric proteinsuccinylate</td>
<td>80 mg</td>
<td>O</td>
<td>Fe³⁺</td>
<td>B03AB09</td>
</tr>
<tr>
<td>fimasartan</td>
<td>60 mg</td>
<td>O</td>
<td></td>
<td>C09CA10</td>
</tr>
<tr>
<td>ceftazidime and beta-lactamase inhibitor¹</td>
<td>6 g</td>
<td>P</td>
<td></td>
<td>J01DD52</td>
</tr>
<tr>
<td>pegteograstim</td>
<td>0.3 mg</td>
<td>P</td>
<td></td>
<td>L03AA17</td>
</tr>
<tr>
<td>opicapone</td>
<td>50 mg</td>
<td>O</td>
<td></td>
<td>N04BX04</td>
</tr>
<tr>
<td>pitolisant</td>
<td>18 mg</td>
<td>O</td>
<td></td>
<td>N07XX11</td>
</tr>
<tr>
<td>doxylamine</td>
<td>25 mg</td>
<td>O</td>
<td></td>
<td>R06AA09</td>
</tr>
</tbody>
</table>

* Administration Route: O = oral; P = parenteral.

¹ ATC level name changed from ceftazidime, combinations. The DDD refers to ceftazidime.

### Changes of DDDs

<table>
<thead>
<tr>
<th>ATC level name/INN</th>
<th>Previous DDD</th>
<th>New DDD</th>
<th>ATC code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DDD</td>
<td>Unit</td>
<td>Adm.R*</td>
</tr>
<tr>
<td>daclizumab</td>
<td>0.35 g</td>
<td>P</td>
<td>5</td>
</tr>
</tbody>
</table>

* Administration Route: O = oral; P = parenteral.