WHO Drug Information

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448 Ceftriaxone sodium
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463 Methylthioninium chloride
468 Methylthioninium injection
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Abbreviations and web sites

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)
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

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

IGDRP generic drug product regulatory gap analysis

The International Generic Drug Regulators Pilot (IGDRP) was launched in 2012 as an international collaborative initiative for information- and work-sharing activities for the regulation and registration of generic drug products. Initially operating as a three-year pilot (2011–2014) the IGDRP was renamed a Programme in 2014, recognizing the progress achieved during the pilot phase, the strong commitment from regulators and their continued interest and need to cooperate to facilitate the timely authorization and availability of safe, effective and high quality generic drug products.

A regulatory gap analysis survey was conducted to identify regulatory similarities amongst the IGDRP members as well as gaps that might create challenges for work-sharing and collaboration. The WHO Prequalification Team, the European Union (EU) and eleven regulatory authorities participated in the survey. The main gaps observed were: the definition of a generic drug product and what is considered to be the same active (or drug) substance; whether and when international reference products can be used in bioequivalence studies; the criteria for granting biowaivers; requirements to use national or regional pharmacopoeias; and the minimum stability data to be included in a generic drug product application at the time of submission.

Introduction
The International Generic Drug Regulator Programme (IGDRP), portrayed in an earlier issue of this journal (1), has the mission to promote collaboration and regulatory convergence in the area of generic drug products in order to strengthen the ability of health authorities to meet their respective mandates. Its goal is to facilitate the timely authorization and availability of safe, efficacious and quality generic drug products.

One of the enablers agreed among IGDRP participants to facilitate work-sharing was the conduct of a regulatory gap analysis survey to identify the similarities and differences in regulatory requirements and practices of participating IGDRP members regarding generic applications.

The gap analysis survey
The survey was led by the Brazilian Health Regulatory Agency (ANVISA). It was divided into four parts:
1. General issues/reference products;
2. Bioequivalence/biowaivers;
3. Quality and good manufacturing practices (GMP); and
4. Other issues.

The gap analysis survey described in this article was led by the medicines regulatory authority of Brazil, ANVISA. We thank Ana Carolina Moreira Marino Araujo and her team at ANVISA for contributing this article on behalf of IGDRP.
Participating organizations
The survey was answered by representatives of the WHO Prequalification Team (WHO-PQT)\(^1\), the European Union regulatory system (referred to as “EU” in this article) and 11 regulatory authorities including: Australia’s Therapeutic Goods Administration (TGA), the Brazilian Health Regulatory Agency (ANVISA), Health Canada (HC), Japan’s Pharmaceuticals and Medical Devices Agency (PMDA), South Korea’s Ministry of Food and Drug Safety (MFDS), Mexico’s Federal Commission for Protection against Sanitary Risks (COFEPRIS), Singapore’s Health Sciences Authority (HSA), South Africa’s Medicines Control Council (MCC), the Swiss Agency for Therapeutic Products (Swissmedic), the Taiwan Food and Drug Administration (TFDA) and the United States Food and Drug Administration (U.S. FDA).

Timelines
The initial gap analysis survey tool was presented during the first IGDRP meeting held in Washington, DC, USA in April 2012. It was agreed that participants should review the tool and provide additional comments.

All organizations had the opportunity to comment on the questions and to update their answers. The data were further evaluated and validated during subsequent meetings and interactions. The results presented in this article reflect updated responses as of April 2016.

Findings

1. General issues/reference products

- **Definition of “generic drug product”**
  All organizations answered that a generic product must fulfil the following criteria: same quantitative and qualitative composition in terms of active (or drug) substance, same (or comparable) dosage form, same route of administration, and bioequivalence with the reference product. However, there were differences in defining what is considered the same active (or drug) substance: The TGA, HC, HSA, MCC, U.S. FDA, EU, Swissmedic and WHO-PQT accept different salts as the same active (or drug) substance as the reference product and there are no safety and efficacy issues with the different form of the active (or drug) substance. ANVISA, COFEPRIS, MFDS, PMDA and TFDA do not consider a different salt to be the same active (or drug) substance.

- **Requirements for reference product**
  The definition of a “reference product” was similar for all organizations: it is the innovator product that has proved its safety, efficacy and quality. However, not all organizations require that the reference product be marketed or registered in their country or region; some permit the use of foreign-sourced reference products (Table 1).

  When the reference product is required to be sourced locally but the original reference product – usually the innovator product – is not available on the market in a country or region, it is necessary to identify a new reference product. The various organizations have different approaches for doing so: TGA, ANVISA,  

\(^1\) WHO Prequalification Team - Medicines; http://apps.who.int/prequal
Regulatory collaboration

HC, PMDA, COFEPRIS, MCC and MFDS use another registered product that has been demonstrated to be equivalent to the original reference product, but the acceptability of this approach is determined on a case-by-case basis and should be carefully justified. Similarly, HSA accepts the use of another registered product based on HSA’s assessment of the product characteristics and the applicant’s justification. In the EU the applicant needs to identify a reference product which is or has been authorized in the EU in accordance with EU legislation (i.e. a marketing authorization must have been granted, but it may have ceased to exist). MCC recommends that the reference product should be purchased from a well regulated market with a stringent regulatory authority participating in the International Council on Harmonization (ICH)². WHO-PQT, which operates supra-nationally, necessarily does not use national reference products. Instead it lists acceptable reference products that may be used in bioequivalence studies and requires that these are purchased from a well regulated market with a stringent regulatory authority participating in ICH, except in those cases where the reference product is not marketed in any ICH member or associated country.

2. Bioequivalence/biowaivers

- **Bioequivalence study sites**
  All organizations except TGA and HC stated that they require the site(s) conducting bioequivalence studies to meet good clinical practice (GCP) standards. TGA and HC responded that, although there is no formal requirement, the site is expected to be in compliance with GCP. It is important to mention that ANVISA, MFDS, COFEPRIS and TFDA require not only that GCP standards should be met, but also that the bioequivalence study site must be certified by the national regulatory authority.

- **Country and population**
  For the PMDA, MFDS and COFEPRIS the bioequivalence studies must be conducted in their country and in their own population (PMDA allows bioequivalence studies to be conducted in Japanese living overseas). The remaining organizations do not have this requirement.

- **Biowaivers**
  All organizations accept biowaivers for generic drug products, but the drug products and drug substances that are eligible vary among the organizations. Biopharmaceutics Classification System (BCS)-based biowaivers are accepted by most of the organizations, with the exception of PMDA. The TGA, HC, EU, COFEPRIS, MCC, U.S. FDA, Swissmedic

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Table 1: Requirements for use of national and international reference products

<table>
<thead>
<tr>
<th>Organizations that require that the reference product be registered in the country or region:</th>
<th>Organizations that allow the use of foreign-sourced reference products in bioequivalence studies</th>
</tr>
</thead>
</table>

* The organizations marked with an asterisk follow a regulation or policy that outlines the criteria for the use of a foreign-sourced reference product, such as proving similarity between domestic and foreign-sourced reference products.

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² [www.ich.org](http://www.ich.org)
and WHO-PQT accept BCS-based biowaivers for Class I and Class III drugs, whereas the MFDS, HSA, ANVISA and TFDA accept BCS-based biowaivers Class I drugs only. ANVISA and TFDA have positive lists of the medicines that are eligible for biowaivers.

All organizations accept biowaivers for additional proportional strengths of immediate-release solid oral drug products that are not included in the in vivo bioequivalence studies, with the appropriate scientific justification.

The IGDRP's Biowaivers Working Group has conducted a specific and more detailed gap analysis on this topic as a mechanism to establish a common set of conditions for granting biowaivers as well as expanding the application of BCS-based waivers, additional strength biowaivers and biowaivers for certain dosage forms (e.g. oral and injectable solutions).

3. Quality and GMP

- **Active pharmaceutical ingredients (API)**

For a generic drug product application there is no limit to the number of API manufacturers that can be included in a single generic drug product application, provided all necessary information is submitted.

Procedures for API evaluation and GMP inspection of API manufacturing sites are summarized in Table 2. Most organizations require confirmation of GMP

<table>
<thead>
<tr>
<th>Organization</th>
<th>API evaluated (a) separately from the drug product</th>
<th>API evaluated with the drug product</th>
<th>GMP inspection must be conducted by the organization itself</th>
<th>GMP certification by another regulatory authority is recognized</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGA</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>ANVISA</td>
<td>Yes (b)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HC</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes (f)</td>
</tr>
<tr>
<td>EU</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes (f)</td>
</tr>
<tr>
<td>PMDA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>MFDS</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>COFEPRIS</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes (f)</td>
</tr>
<tr>
<td>HSA</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>MCC</td>
<td>No</td>
<td>Yes</td>
<td>No (d)</td>
<td>No</td>
</tr>
<tr>
<td>Swissmedic</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes (e)</td>
</tr>
<tr>
<td>TFDA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>WHO-PQT</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>U.S. FDA</td>
<td>Yes (c)</td>
<td>No</td>
<td>Yes (e)</td>
<td>Yes (g)</td>
</tr>
</tbody>
</table>

(a) In this context the word “evaluated” is used in the same sense as the word “registered” or “authorized”.  
(b) Applies only to the 30 APIs on the positive list, other APIs are evaluated with the drug product.  
(c) When the sites are separated  
(d) GMP inspection not mandatory  
(e) Yes, for domestic sites. For foreign sites, U.S. FDA relies on partnership arrangements with other regulatory authorities in limited cases.  
(f) HC, EU and COFEPRIS accept GMP certification from countries with which mutual recognition agreements have been signed.  
(g) U.S. FDA considers a full inspection report rather than a GMP certificate.
compliance for API manufacturing sites, and many require that the inspection must be conducted by their own inspectorate. Some IGDRP members recognize GMP certification by other authorities, such as stringent regulatory authorities (SRA) or regulatory authorities of countries with which mutual recognition agreements have been signed.

The organizations use different procedures to evaluate the quality information related to the manufacture and control of APIs. Some authorize APIs separately from the drug product, others do so in connection with the marketing authorization application for the drug product, and in some cases both procedures are possible.

The TGA, HC, EU, HSA, MCC, Swissmedic, TFDA and WHO-PQT recognize the European Directorate for the Quality of Medicines – EDQM’s certificate of suitability (CEP) and do not duplicate the assessment of the API information covered by the CEP.

- Stability studies

In general, stability studies are conducted as per the requirements for the specific climatic zones (Zones I, II, III, IVA and IVB) that reflect a country’s climate (2). Most IGDRP members follow the recommendations of the ICH Q1A guideline (3). Three exceptions are HSA, ANVISA and WHO-PQT. These organizations require finished product stability studies conducted in Zone IVB; HSA follows the ASEAN Guideline on Drug Product Stability Data (4), ANVISA follows its national guidelines for stability studies (5), and WHO-PQT follows WHO stability guidelines (6).

All organizations require the stability study to be conducted with the drug substance or the drug product in its primary package. If the secondary package has a protective or functional effect, the study may be conducted in this package.

ANVISA and TGA require additional stability studies for the API in their own climatic zone if it is imported from a country in a milder climatic zone. HSA evaluates the stability impact of the API in the drug product stability studies and does not require additional stability studies for the API.

If there are multiple API or finished pharmaceutical product (FPP) manufacturing sites proposed for registration, TGA, WHO-PQT, ANVISA, COFEPRIS, HSA, TFDA and MCC require stability data from all API–FPP site combinations but TGA, WHO-PQT, HSA, MCC and TFDA accept science-based justification for not requiring all combinations of stability data. HC, EU, PMDA, MFDS and Swissmedic do not require the stability studies to be conducted with all API–FPP site combinations. For PMDA, stability data for the API-FPP combination prepared using the main manufacturing route must be presented, and the stability data for other manufacturing routes must be confirmed at the applicant’s own responsibility.

Information on the number of batches and minimum number of months of stability data to be presented for a general case in a generic drug product application is summarized in Table 3.
Table 3: Minimum stability data required at the time of filing a generic product application

<table>
<thead>
<tr>
<th>Organization</th>
<th>Number of batches: API</th>
<th>Number of batches: drug product</th>
<th>Accelerated stability data</th>
<th>Long term stability data</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGA</td>
<td>2 pilot or commercial scale</td>
<td>2 pilot or commercial scale</td>
<td>6 months</td>
<td>6 or 12 months depending on dosage form</td>
</tr>
<tr>
<td>ANVISA</td>
<td>3</td>
<td>3 pilot or commercial scale</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>HC</td>
<td>2 (a)</td>
<td>2 (a)</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>EMA</td>
<td>3 pilot or commercial scale</td>
<td>3 pilot or commercial scale</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>PMDA</td>
<td>0</td>
<td>3</td>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td>MFDS</td>
<td>3</td>
<td>3</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>COFEPRIS</td>
<td>3</td>
<td>3</td>
<td>3 months</td>
<td>6 months</td>
</tr>
<tr>
<td>HSA</td>
<td>3</td>
<td>2 or 3 (c)</td>
<td>6 months</td>
<td>6 or 12 months (c)</td>
</tr>
<tr>
<td>MCC</td>
<td>2</td>
<td>2</td>
<td>3 months</td>
<td>9 months</td>
</tr>
<tr>
<td>Swissmedic</td>
<td>3 pilot or commercial scale</td>
<td>2 pilot or commercial scale</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>TFDA</td>
<td>3</td>
<td>3</td>
<td>6 months</td>
<td>6 months at application + 12 prior to authorization</td>
</tr>
<tr>
<td>WHO-PQT</td>
<td>3</td>
<td>2</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>U.S. FDA</td>
<td>3 pilot or 2 pilot + 1 small scale (b)</td>
<td>3 pilot or 2 pilot + 1 small scale</td>
<td>6 months</td>
<td>6 months at the time of submission (e)</td>
</tr>
</tbody>
</table>

(a) Reflects requirement at the time of the survey; this requirement was subsequently changed to 3 batches in an updated quality guidance document.
(b) If the size of the pilot scale batch does not follow ICH recommendations, the applicant should provide a justification.
(c) 2 batches of 6 months for stable API and conventional dosage form; 3 batches of 12 months for unstable API or critical dosage form
(d) For reproductive health products and second-line tuberculosis products an exception can be made to require only 3 months accelerated and long-term data at the time of submission.
(e) The Abbreviated New Drug Application (ANDA) should be updated with 12 months of long-term data during the review cycle.

- **Imported drugs**
  The organizations have different requirements for imported drugs regarding responsibility for batch release analysis and mandatory marketing authorization in the country of origin (Table 4).

- **Acceptable standards and pharmacopoeias**
  All participants have specific guidelines related to quality and validation, and they also adopt international guidelines, such as those of ICH, officially or in principle. ANVISA is the only agency that does not officially adopt ICH guidelines, whilst the MCC generally accepts reference to ICH guidelines. Besides ICH guidelines, HSA also officially adopts the ASEAN guideline.
  The adoption of regional or national pharmacopoeias is mandatory for PMDA and COFEPRIS. For the other organizations it is not mandatory to use the national pharmacopoeia; they recognize other pharmacopoeias besides their own, for example the United States Pharmacopeia (USP), the British Pharmacopoeia (BP) and/or the European Pharmacopoeia (Ph Eur).
Table 4: Requirements for imported drugs

<table>
<thead>
<tr>
<th>Organization</th>
<th>Quality control must be performed by the manufacturer</th>
<th>Quality control must be performed by the importer</th>
<th>The product must have marketing authorization in the country of origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGA</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>ANVISA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>HC</td>
<td>No (a)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>EMA</td>
<td>No</td>
<td>Yes (d)</td>
<td>No</td>
</tr>
<tr>
<td>PMDA</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>MFDS</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>COFEPRIS</td>
<td>Yes (b)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>HSA</td>
<td>Yes (c)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>MCC</td>
<td>Yes (b)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Swissmedic</td>
<td>No (a)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>TFDA</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>WHO-PQT</td>
<td>Yes</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>U.S. FDA</td>
<td>Yes</td>
<td>No (e)</td>
<td>No</td>
</tr>
</tbody>
</table>

(a) Testing for release purposes can be performed by an alternate testing facility provided it is GMP-compliant.
(b) COFEPRIS and MCC allow testing exemption for the importer if the transport temperature and humidity is monitored.
(c) For import of only the first batch after approval, applicant must provide quality control of that batch for review.
(d) Medicinal products coming from third countries must undergo a full analysis in an EU Member State. This requirement may be waived where arrangements between EU and exporting country exist ensuring GMP standards at least equivalent to those in the EU.
(e) Unless the importer is finishing the processing of the API or drug product (in which case the importer becomes a manufacturer).

When compendial analytical procedures exist, their adoption is mandatory for PMDA and COFEPRIS; it is not mandatory for TGA, ANVISA, HC, EU, HSA, MCC, MFDS, Swissmedic, TFDA and WHO-PQT. However, HC, EU, MCC, Swissmedic and WHO-PQT require that the results of a comparison/equivalency study between the compendial and in-house analytical procedures are provided if a compendial standard is claimed but an in-house analytical method is used.

Regarding the use of primary standards, PMDA recommends their use if they are listed in the Japanese Pharmacopoeia. ANVISA requires their use in the validation procedure. TGA, HC, EU, TFDA, MFDS, COFEPRIS, HSA, MCC, WHO-PQT and Swissmedic accept the use of secondary reference standards with appropriate justification (e.g., standardized against a primary standard).

4. Other issues

- Work-sharing and cooperation
  A few organizations have systems for work-sharing and cooperation in place. The EU has two procedures where authorizations are agreed by Member States: the decentralized procedure (simultaneously) and the mutual recognition procedure (sequentially). In addition, some generic drug products are authorized through the centralized procedure by the European Commission. Swissmedic, HC, TGA and HSA have
a cooperation procedure under the Australia-Canada-Singapore-Switzerland Consortium Generics Initiative (the ACSS Consortium), and HSA also has bilateral agreements for work-sharing on generic drug products with Malaysia. HC is engaged in a number of multi-lateral and bilateral international cooperation activities regarding generic products but does not have any mutual recognition agreements with any other regulatory authority for the assessment of generics.

- **Performance targets**
  All organizations have set performance targets or time limits for the assessment of generic drug product applications. It is important to identify these performance targets for the work-sharing process. One of the enablers of the IGDRP is the construction of a timeline with time limits and detailed milestones.

- **Common Technical Document (CTD)**
  The TGA, HC, EU, HSA, MCC, MFDS, Swissmedic, U.S. FDA, TFDA and WHO-PQT have officially adopted ICH’s Common Technical Document (CTD) format for generic drug product applications (7). PMDA, COFEPRIS and ANVISA have specific formats that are similar to the CTD.

- **Prioritization mechanisms**
  ANVISA, HC, PMDA, MFDS, COFEPRIS, HSA, MCC, U.S. FDA and WHO-PQT have mechanisms to prioritize generic drug product applications based on public health interests, considering factors such as drug shortages and governmental policies.

- **Intellectual property provisions**
  All IGDRP members have data protection and/or exclusivity periods before a generic drug product can be marketed. These periods vary from 5–20 years.

**Discussion**

While the participating organizations’ definitions of a “generic drug product” all appear similar, their definitions of “the same active (or drug) substance” differ. Some organizations accept different salts, esters and ethers as the same API as long as they have the same active moiety, while others do not. A product could therefore be considered a generic drug product in one country or region but not in another. This issue was identified as a gap. Solving it would enable greater information-sharing in the assessment of generic drug product applications.

The use of a foreign-sourced reference product is allowed by some organizations but not by others. Differences among IGDRP members in requirements for the reference product and documentation supporting the bioequivalence of a generic drug product were also identified as a gap. In this regard, the IGDRP concluded that it would be easier to start work-sharing activities with drug products that are eligible for a biowaiver, e.g., oral and injectable solutions.

All organizations accept biowaivers for generics, but the criteria for a drug product to be eligible for a biowaiver vary among them. This gap is being discussed in more detail in the IGDRP Biowaivers Working Group. A scientifically based discussion to work towards convergence and harmonization is in progress.

A further gap was identified regarding the minimum stability data – i.e., numbers of API and drug product batches to be tested, and the minimum number of months of accelerated and long-term stability data – that are required at the time of submitting the application. These
Regulatory collaboration

differences may delay the filing in certain countries, thus complicating the work-sharing among organizations.

The IGDRP members that participated in the survey are representative of the world’s regions and their different climatic zones. The conduct of stability testing according to the relevant climatic zone is indispensable, and the different requirements are scientifically based and justified. For applications filed globally, additional or complementary data must be provided by the applicant as appropriate.

Different procedures are used by the IGDRP members for the assessment of APIs. Some organizations authorize APIs separately from the drug product, others authorize them in conjunction with the drug product, and in some cases both pathways are possible. However, the differences observed in the survey were mostly related to organizational working procedures and do not hamper the work-sharing activities.

The requirement to use the national or regional pharmacopoeia of the country of application is a challenge for a globalized industry, since the use of different analytical procedures and acceptance criteria in different countries or regions will cause duplication of efforts. Differences in pharmacopoeial requirements complicate cooperation and collaboration.

Conclusion
The gaps observed in the survey warrant reflection on the reasons for the different requirements. If they are not scientifically justified, discussions on common practices should be stimulated within and among organizations.

References
1 The International Generic Drug Regulators Pilot. WHO Drug Information 2014; 28(1); 3-10.
5 ANVISA. Resolução - RE nº 1 de 29/07/2005.
Generic medicines

Interchangeability of WHO-prequalified generics

Generic medicines can enable huge cost-savings as they create competition, driving down prices. In medicines regulation and in WHO prequalification, the efficacy of generics is demonstrated by bioequivalence studies.

WHO medicines prequalification has facilitated academic research, and has itself been a subject of academic research. Adjusted indirect comparisons were conducted, using the results of separate bioequivalence studies for WHO-prequalified generics against the same comparator product. The comparisons found that the generics can be considered as clinically equivalent among each other. Recommendations are provided for regulatory assessment of generics in WHO Member States and for possible approaches to harmonization of bioequivalence requirements to facilitate access to needed products.

Impact of generics in public health

Use of generic medicines significantly reduces the cost of medicines to both governments and patients. Generic medicines are those produced without a licence from the innovator company when the patent or other market exclusivity rights on the innovator product has expired.

A striking example of the impact of generics is the evolution of prices on the antiretroviral (ARV) market. The median price per patient per year of first-line ARV therapy dropped from about US$10 000 to less than US$100 with the introduction of generic FDCs, enabling the scaling-up of access to antiretroviral therapy from 0.5 million people on ARVs in 2003 to 15.8 million globally in 2015 (1).

Bioequivalence assessment

Approval of a generic medicine is based on the demonstration of interchangeability or therapeutic equivalence to the innovator through bioequivalence studies. Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same dose.

The requirement of bioequivalence studies for generics in lieu of clinical efficacy and safety studies was introduced in

This review article is based on a PhD thesis by Luther Gwaza titled “Adjusted indirect comparisons of bioequivalence studies”, which was defended at Utrecht University on 8 July 2016. The research presented in the PhD thesis was conducted under the umbrella of the Utrecht WHO Collaborating Centre for Pharmaceutical Policy and Regulation (www.pharmaceuticalpolicy.nl), which is based at the Division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University in the Netherlands. The Collaborating Centre aims to develop new methods for independent pharmaceutical policy research, evidence-based policy analysis and conceptual innovation in the areas of policy-making and evaluation in general.
in the United States (U.S.) in 1984 and is now a widely accepted regulatory standard. By applying this approach to ARVs, including fixed-dose combinations, the WHO Prequalification Programme was instrumental in scaling up global access to safe, efficacious, quality ARV treatment at affordable cost in the early 2000s (2).

**Adjusted indirect comparisons**

Bioequivalence studies compare a generic product with a comparator product, usually the innovator product. However, in practice, it is not unusual for generics of the same drug to be interchanged between each other. Performing direct comparisons between all available generics of the same drug is not feasible. Therefore, adjusted indirect comparisons were performed among WHO-prequalified generics, using data from independent bioequivalence studies conducted against the same comparator product. A total of 59 generic products were compared in two published studies (3, 4) and one study submitted for publication (Figure 1).

Figure 1: Pharmacokinetic parameters for WHO-prequalified generics

![Pharmacokinetic parameters for WHO-prequalified generics](image)

A. Original results (examples)

**Artemether / Lumefantrine**

<table>
<thead>
<tr>
<th>Equation</th>
<th>Source</th>
</tr>
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<tbody>
<tr>
<td>AUC(0-t)</td>
<td>Source: (3)</td>
</tr>
<tr>
<td>C_{max}</td>
<td>Source: (4) Also compared, results not shown: Ethambutol, pyrazinamide, isoniazid</td>
</tr>
</tbody>
</table>

**Rifampicin**

<table>
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<tr>
<th>Equation</th>
<th>Source: (4) Also compared, results not shown: Efavirenz, tenofovir, emtricitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-t)</td>
<td>±15%</td>
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<tr>
<td>C_{max}</td>
<td>±10%</td>
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**Lamivudine**

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<tr>
<th>Equation</th>
<th>Source: (4) Also compared, results not shown: Efavirenz, tenofovir, emtricitabine</th>
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<tr>
<td>AUC(0-t)</td>
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<td>C_{max}</td>
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AUC(0-t) = Area under the time-concentration curve; C_{max} = Peak plasma concentration

Different symbols represent different WHO-prequalified generics.

**B. Indirect comparisons**

- Different computational methods were explored to investigate the ability of indirect comparisons to demonstrate the interchangeability of generics.
- The WHO-prequalified generics were found to be not only bioequivalent with the comparator, but also interchangeable among each other without safety / efficacy concerns.
- The ability of indirect comparisons to demonstrate interchangeability between generics was found to be dependent not only on the real differences between the products, but also on the design of the original bioequivalence (BE) studies being combined. The findings could be used to consider further requirements for BE studies in situations when interchangeability (switchability) of generics is critical (5).
The results show that the different WHO-prequalified generics included in each study can indeed be considered as clinically equivalent.

**Regulatory assessment of generics: the example of Zimbabwe**

**Uptake of generics**

The use of generic products is a national responsibility. Registration of generic products and generic substitution policies are well advanced in high-income countries, but are still under development in low- and middle-income countries. WHO is providing norms and standards for medicines quality assurance in Member States, including resource-constrained ones. Nonetheless, in many countries the demonstration of interchangeability remains non-existent or is not fully enforced. Likewise, some pharmaceutical manufacturers in these countries are inexperienced in performing bioequivalence studies to the required regulatory standard.

Even where regulatory review is done according to WHO-recommended standards, including those on demonstration of interchangeability for generics (6), regulatory resource constraints may hinder the uptake of generic products. An analysis of the regulatory system in Zimbabwe\(^1\) showed that the number of marketing authorization applications received exceeds the available regulatory capacity, resulting in long timelines to approval. In the period from 2003–2015 a total of 2,083 applications were received, and 1,002 products were approved, while the rest were either pending or refused registration. The overall median time from application to registration of a product was 710 days (inclusive of manufacturers’ time to respond to queries), with an interquartile range of 422-1065 days.

**Collaborative approaches**

Collaboration and information-sharing between regulatory authorities are the most resource-efficient strategies to ensure access to medicines, particularly in resource-constrained settings. Harmonization and work-sharing approaches are being implemented in all regions of the world, including the regional economic communities in Africa.

Since 2012, Zimbabwe participates in the WHO collaborative procedure for registration of WHO-prequalified products, which has been taken up by 27 countries including 21 African countries at the time of writing\(^2\). This procedure entails granting of national marketing authorizations based on a verification that the product is technically the same as prequalified by WHO.

Since 2013, a regional collaborative medicine registration process named Zazibona\(^3\) is practised among Botswana, Namibia, Zambia and Zimbabwe. Applicants submit dossiers to at least two of the four participating authorities. Assessment is done jointly with one authority as rapporteur, leading to simultaneous registration in all relevant countries. WHO provides an electronic platform for information exchange and facilitation support.

Zazibona has enabled product approval with reduced timelines. A review of


\(^2\) [http://apps.who.int/prequal/info_applicants/collaborative_registration_main.htm](http://apps.who.int/prequal/info_applicants/collaborative_registration_main.htm)

\(^3\) [www.mcaz.co.zw/index.php/downloads/category/21-zazibona](www.mcaz.co.zw/index.php/downloads/category/21-zazibona)
documents for 85 applications considered from October 2013 to December 2015 showed that 32 had received a positive opinion, 15 had received a negative opinion, 10 were withdrawn by the respective applicant, 25 were awaiting responses from applicants and 3 were under review. The total review time, including the time for applicants to respond to questions, amounted to a median of 10.3 months for a positive recommendation – with an additional 1.5 months until final approval – and 12.4 months for a negative opinion. The main reasons for negative opinions were failure to respond to requests for additional information or incomplete submissions (50%), and bioequivalence-related deficiencies (40%).

Key success factors in the Zazibona initiative have been identified, including ownership, effective leadership, partner resources including co-financing, a cost-efficient model, social capital, clear roles and structure, effective communication and demonstrable results. On the other hand, a monitoring and evaluation framework, committed funding and institutionalization are still required to ensure sustainability. Overall, the Zazibona initiative can be considered as an effective collaborative mechanism to facilitate rapid access to needed medicines, and could serve as a model to be followed by other developing countries.

Selection of comparator product
Collaboration critically depends on harmonized regulatory systems. A major barrier for global harmonization with respect to generic medicines – and for the adjusted indirect comparisons described earlier – is the difficulty to use a common comparator product globally. Despite considerable progress in harmonizing regulatory requirements for bioequivalence studies, disparities remain with respect to the requirements for comparator products.

WHO recommends that the comparator product should be, in order of priority: 1) an innovator product available on the local market, 2) the national market leader, 3) a WHO comparator, 4) an innovator product imported from an ICH country, and 5) a generic product approved in an ICH country (7). WHO recommends against using a generic product as a comparator as long as an innovator pharmaceutical product is available, because this could lead progressively to less similarity between products, a phenomenon called “biocreep”.

Most countries follow these general principles and require the comparator product to be obtained from their national markets to ensure that the generics will be interchangeable with the comparator as well as among each other. Some countries accept a comparator from a foreign market, provided there is in vitro demonstration of similarity with the local comparator.

For pharmaceutical companies however, conducting specific bioequivalence studies for each country makes economic sense only if the market size is large. Thus, the recommendation to use a local comparator is impractical in many settings, particularly in LMICs which often have very small market sizes.

In the context of regional harmonization it may be found advantageous to establish a regional comparator product for which quality, safety and efficacy has been established. For example in the European
Union the innovator product as marketed in different EU countries is considered to be the same because its approval is based on the same documentation proving efficacy and safety; it would therefore be acceptable in all countries. In recent years, the cooperation approach has been extending beyond the EU system with the International Generic Drug Regulators Programme (IGDRP) pilot for generic medicines (see also the article on page 361), with a working group on bioequivalence looking at some of the specific issues mentioned in this paper.

It is acknowledged that differences may exist between the innovator product in one market and the same innovator product in other markets5. To ensure the similarity of comparator products, NMRAs could compare their qualitative and quantitative composition, specifications, manufacturing site and process to see whether the products are sufficiently similar, and could make that information public.

Acceptance of foreign or international comparators would reduce the number of in vivo bioequivalence studies needed, saving resources that could be spent on more in-depth studies for example under fasting and fed conditions, on different strengths of a product, or in patients under real conditions of use.

WHO prequalifies generics for supply to multiple countries, especially LMICs, where they are often accepted by NMRAs without requiring any further studies with a local comparator product. Therefore, the experience of WHO PQT provides insights on how to identify and obtain an acceptable comparator product in a global context.

Conclusions and recommendations

The indirect comparisons described earlier in this paper have shown that WHO-prequalified generics may be interchanged among each other without any safety and efficacy concerns. This is pivotal in supporting generic prescribing and substitution policies, which are important to increasing access to medicines.

However, these findings cannot necessarily be extrapolated to other nationally approved products, especially in resource-constrained settings. Although NMRAs should ensure that generic products are interchangeable before granting approval, they may have different requirements and review practices, and many have significant limitations of capacity and resources.

Harmonized requirements for bioequivalence and comparator products are critical for collaboration. It must be noted that this approach works only among countries applying similar and consistent standards in line with WHO guidelines, which may not be the case in most Sub-Saharan African countries.

Nevertheless, the WHO prequalification approach for demonstration of bioequivalence could be followed as a global approach. This is done in the collaborative registration procedure, where

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5 For example, carbamazepine (Tegretol®) in the U.S. is different from carbamazepine (Tegretol®) approved in Europe. This is because the product has evolved separately in the two jurisdictions after the clinical trials, at a time when demonstration of bioequivalence was not yet required for the approval of changes. Carbamazepine is an antiepileptic with narrow therapeutic index, and differences between the reference products could mean that generics approved as bioequivalent to one or the other reference product are not necessarily interchangeable. The European reference product is therefore not acceptable in the U.S. and vice versa. In the specific case of Tegretol® the manufacturer has developed an in vitro-in vivo correlation, so that a simple dissolution test can provide information about the similarity between these products.
the outcomes of bioequivalence studies submitted to WHO are accepted without further comparisons of their comparator product against the national one. Similarly, in the Zazibona collaborative initiative, the WHO prequalification approach for selecting comparator products is applied, and one bioequivalence study is sufficient for all four countries.

To verify generic interchangeability, the adjusted indirect comparison approach described earlier in this paper could be used to support evidence-based clinical decisions by healthcare professionals. To enable such comparisons, the regulators should consider making data from approved bioequivalence studies publicly available. For situations when high assurance of interchangeability among generics is critical, for example for medicines with a narrow therapeutic index, regulators may wish to apply stricter national requirements for bioequivalence.

References


Adopted guidance

WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce: Questions and Answers (Q & A)

This is a revision of a WHO guidance document as adopted by the Expert Committee for Specifications on Pharmaceutical Preparations at its 50th Meeting held in October 2015. The meeting report is available at www.who.int/entity/medicines/publications/pharmprep/trs_996/en/index.html. Prior to its adoption the text was posted for public comment on the WHO web site as Working Document QAS/15.623, June 2016. WHO guidance related to the Certification Scheme is available at www.who.int/medicines/areas/quality_safety/regulation_legislation/certification.

Background

The WHO Certification Scheme for finished pharmaceutical products is an international voluntary agreement to provide assurance to countries participating in the Scheme, about the quality of pharmaceutical products moving in international commerce (World Health Assembly resolution WHA22.50 (1969), World Health Assembly resolution WHA28.65 (1975), World Health Assembly resolution WHA41.18 (1988), World Health Assembly resolution WHA45.29 (1992), World Health Assembly resolution WHA50.3 (1997). The primary document of the Scheme was the Certificate of Pharmaceutical Product (CPP). The WHO Expert Committee on Specifications for Pharmaceutical Preparations, during its forty-third meeting, recommended that the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce should be reviewed in light of the changing environment, including the rapid globalization of the pharmaceutical manufacturing sector coupled with changes in the make-up of both the regulators and the groups involved in procurement. Any change of the Scheme will necessitate a discussion by Member States.

In addition, as an interim measure, the Expert Committee also requested that a questions and answers (Q & A) document on the function of the Scheme should be prepared (see WHO Technical Report Series, No. 953, pp. 47–48 (2009)). The previous version of the Q & A document (working document QAS/10.374) was prepared and is available on the web as follows: http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/gas_certif_scheme_2012.pdf?ua=1.

We thank the CPP Network Team of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) for preparing the working document that formed the basis of the review through the Expert Committee’s consultative process.
The following is a collection of questions and answers relating to the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce¹ and specifically to the CPP.

The “WHO Certification Scheme”

• represents WHO activity on the quality, and potentially the safety and efficacy of pharmaceutical products moving into international commerce
• is an administrative instrument which enables WHO Certification Scheme Member States to request certain information from another WHO Certification Scheme Member State by means of defined documents, i.e. a CPP.

The CPP gives a snapshot of the regulatory status of a pharmaceutical product and of the CPP applicant in the certifying country. It is for a single product only, since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

For easier reference, questions have been grouped into the following categories to support the review process.

[Click on red links to navigate]

1. About the WHO Certification Scheme
2. Related to issuing country
3. Related to recipient country
4. GMP status
5. Alternatives to a CPP

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   1.Q2 Why is it called the WHO Certification Scheme?
   1.Q3 When was the Scheme developed?
   1.Q4 How can a WHO Member State or regional organization be eligible for participation in the Scheme?
   1.Q5 Where can one find the list of organizations and countries party to the Scheme?
   1.Q6 Does the list of Member States and organizations party to the Scheme provide the names and addresses of those government organizations authorized to sign and issue a Certificate for a Pharmaceutical Product (CPP)?
   1.Q7 How can the Scheme facilitate trade in pharmaceutical products?
   1.Q8 How does the Scheme operate?
   1.Q9 Is the Scheme mandatory?
   1.Q10 Is there any written document that provides detailed information on the WHO Certification Scheme?
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   1.Q13 Is there a standard format for CPPs?
   1.Q14 What should recipient countries do in case of any doubt about a CPP?
   1.Q15 Are certifying authorities penalized if they issue CPPs, but do not meet WHO requirements for self-certification and subsequent issue of CPPs?
   1.Q16 What are the main problems encountered in the application of the Scheme?

¹ Later also referred to as the “WHO Certification Scheme".
2. Related to issuing country

2.Q1 Does WHO issue CPP?
2.Q2 Can any one issue a CPP?
2.Q3 What should Member States and regional organizations possess in order to issue a CPP to support the export pharmaceutical products?
2.Q4 Should a CPP issued by Member States bear the WHO emblem or the acronym WHO?
2.Q5 By whom is a CPP issued and for what requirement in the recipient authority?
2.Q6 Is the CPP evidence of quality, safety, efficacy review and approval?
2.Q7 What is the significance of the declaration of marketing status, i.e. whether the product is actually on the market in the exporting country?
2.Q8 Imagine a situation in which a product is authorized for marketing in the country of manufacture, but is not actually available on the market. Can the competent authority of the exporting country issue a CPP to support export?
2.Q9 Sometimes a country may wish to import a special dosage form, strength or formulation of a certain known product, and this particular product may not be registered in the manufacturing country. Under such circumstances, can the authority of the exporting country issue a CPP?

3. Related to recipient country

3.Q1 When would a CPP be required?
3.Q2 Is it a must that a pharmaceutical product has to be exported from the same country as the certifying authority?
3.Q3 Is it possible to obtain a CPP from a certifying authority that is not the country where the manufacture of the finished product takes place?
3.Q4 Is it necessary for the CPP to come from the country where finished product manufacture takes place?
3.Q5 Should recipient authorities require a CPP from more than one certifying authority?
3.Q6 Business Process Scenario Questions for when a product is contract manufactured?
  3.Q6.1 Is contract manufacturing accepted?
  3.Q6.2 In case of a contract-manufactured product: from which country should the authority in the importing country (recipient authority) accept the Certificate for a Pharmaceutical Product (CPP)?
3.Q7 Can a CPP also be used to provide evidence of an administrative review and approval (e.g. as certification of acceptability of a company name change)?
3.Q8 Is it necessary to legalize the CPP?

4. GMP status

4.Q1 Is it necessary for recipient authorities to require GMP certificates in addition to a CPP?
4.Q2 Does the CPP provide evidence of GMP?
4.Q3 What is the difference between approval of the quality data in the submission and evidence of GMP?
4.Q4 When a CPP forms part of a regulatory review, is it necessary to conduct a site inspection as well?

5. Alternatives to a CPP

5.Q1 Are there any alternatives to a CPP as evidence of approval by a national medicine regulatory authority (NMRA)?
5.Q2 When and by whom is a statement of licensing status of pharmaceutical product(s) (SLSPP) issued?
5.Q3 What is a batch certificate?

6. Glossary
1. About the WHO Certification Scheme

1.Q1 What is the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce?

1.A1 It is a Scheme developed by the World Health Organization (WHO) in response to the request of WHO Member States to facilitate international trade in pharmaceutical products between Member States and it gives guidance to the issuing as well as requesting health authorities.

1.Q2 Why is it called the WHO Certification Scheme?

1.A2 It is called the WHO Certification Scheme because it was developed by WHO in response to the request of Member States.

1.Q3 When was the Scheme developed?

1.A3 It was first developed in 1975. Since then it has been revised in 1988, in 1992 and in 1997.

1.Q4 How can a WHO Member State or regional organization be eligible for participation in the Scheme?

1.A4 Any WHO Member State or regional organization intending to participate in the Scheme may do so by notifying the Director-General of WHO in writing, of its willingness to participate in the Scheme; any significant reservations it intends to observe relating to this participation; and by providing the names and address of its national medicines regulatory authority (NMRA) or other competent authority.

1.Q5 Where can one find the list of organizations and countries party to the Scheme?

1.A5 WHO publishes the names and addresses of Member States party to the Scheme. The list is available on the WHO website: http://www.who.int/entity/medicines/areas/quality_safety/regulation_legislation/certification/contacts/en/index.html. A hard copy of the list is also published and distributed to Member States. The list is updated from time to time.

1.Q6 Does the list of Member States and organizations party to the Scheme provide the names and addresses of those government organizations authorized to sign and issue a Certificate for a Pharmaceutical Product (CPP)?

1.A6 Yes, the list provides the names and full addresses of those government organizations authorized to sign and issue a certificate for a pharmaceutical product (CPP). NMRAs receiving a CPP can use this list to check and verify if the certificate they are receiving has been issued by the authorized organization.

1.Q7 How can the Scheme facilitate trade in pharmaceutical products?

1.A7 The Scheme is an administrative instrument that requires a competent authority of a participating Member State (the certifying country), upon application by a commercially-interested party (the applicant company), to certify/attest to the competent authority of another participating Member State (the recipient country) that:

• a specific pharmaceutical product is authorized for marketing in the certifying country, or if not, the reason why authorization has not been accorded;
• confirmation of marketing status in issuing country;
• the manufacturing facilities and operations conform to good manufacturing practices (GMP) as recommended by WHO.

1.Q8 How does the Scheme operate?
1.A8 The Scheme operates as follows:
• the certificate recipient authority has in its national medicine legislation or guidelines a requirement for the submission of a CPP for products being imported into the country as a support to ensure the quality of the product being imported (in most countries the CPP forms part of the dossiers to be submitted to NMRA to have a product registered by the authority);
• the applicant/importing company requests a CPP from the certifying authority through the exporting company;
• the certifying authority issues a CPP to the importing/applicant company via the exporting company. The practice at present is as shown in the diagram below.

![Diagram of Scheme operation]

At the time of the development of the Scheme the understanding was that the issuing authority would send the CPP directly to the recipient authority.

1.Q9 Is the Scheme mandatory?
1.A9 No, the Scheme is not mandatory. It is a voluntary agreement devised to enable countries with limited medicine regulatory capacity to obtain partial assurance from exporting countries concerning the quality, safety and efficacy of the pharmaceutical product they plan to import.

1.Q10 Is there any written document that provides detailed information on the WHO Certification Scheme?
1.A10 Yes, there are published guidelines called “Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce”. One can access these guidelines by going to the WHO website: [http://www.who.int/entity/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/index.html](http://www.who.int/entity/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/index.html).

1.Q11 What products are covered under the WHO Certification Scheme?
1.A11 Pharmaceutical products covered under the Scheme are:
• finished pharmaceutical products (FPPs) intended for administration to human beings;
• pharmaceutical products intended for administration to food-producing animals;
• active pharmaceutical ingredients (APIs).
• There is now a separate scheme called the WHO pharmaceutical starting materials certification scheme (SMACS) which has guidelines on importation of APIs (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/gas_certif_scheme_2012.pdf?ua=1).

1.Q12 What are the different types of certificates that can be requested within the scope of the Scheme?
1.A12 Three types of certificate can be requested for pharmaceutical products within the scope of the Scheme:
• a CPP or product certificate;
• a statement of licensing status of pharmaceutical product(s);
• a batch certificate of pharmaceutical product.

Further information is given in Section 5, alternatives to the CPP.

1.Q13 Is there a standard format for CPPs?
1.A13 Yes, there is a standard format. The WHO standard format was last agreed by WHO Member States in 1997 (reference: WHO guidelines, Section 3.2). The template gives a numbering which is followed by almost all certifying countries. They state this on the top of the CPP. Also the explanatory notes attached to the CPP are almost the same in every certifying country:
• the standard WHO format for CPPs facilitates understanding and review by the recipient authority. It obliges certifying authorities to disclose important information to the importing country;
• by keeping the numbering of the WHO template recipient authorities can easily retrieve the information in the CPP;
• since CPPs are often issued bilingually, the text style may look differently by having the national language and the translation organized in columns, or the translation written in italic letters follows every sentence of national language;
• there may be different mandatory/optional attachments upon request in addition to the CPP, such as quantitative composition, the summary of product characteristics, the package insert label, etc., depending on the perspective and the legislation of either the certifying or the recipient country;
• recipient authorities should refrain from obtaining data other than in the WHO standard format or in addition to the standard CPP format;
• certifying authorities should not issue the outdated “free sales certificates”. These have been replaced by the WHO format CPP.

1.Q14 What should recipient countries do in case of any doubt about a CPP?
1.A14 In case of any doubt the competent authorities of recipient countries should communicate directly with the authorized body that has issued the certificate or contact WHO regional branch to clarify the matter.

1.Q15 Are certifying authorities penalized if they issue CPPs, but do not meet WHO requirements for self-certification and subsequent issue of CPPs?
1.A15 No, there is no system to penalize them. WHO does not have the power to certify, inspect or penalize certifying authorities. Since the Scheme is voluntary, Member States party to the Scheme self-certify their compliance.
1.Q16 What are the main problems encountered in the application of the Scheme?
1.A16 A number of problems have been encountered in the use of the Scheme, which include:

- countries not party to the Scheme issue certificates;
- authorities that do not meet the requirements or format stated in the guidelines for the Scheme when they issue CPPs;
- some issuing authorities put the WHO emblem, logo or acronym on the certificate, thereby creating the impression that the certificate is authenticated by WHO;
- certifying authorities limit the CPP to products manufactured and exported from the certifying country;
- the CPP is no longer recognized to substitute the full dossier and QSE;
- GMP status given in the CPP is no longer enough for the recipient countries and additional GMP certificates are requested;
- there is a lack of understanding that the CPP reflects the approval status of the certifying country only;
- CPPs can be a prerequisite for a regulatory submission rather than being provided just prior to approval;
- the lead times of the certifying authorities can be very long, sometimes several months;
- the way to apply for a CPP is not harmonized as every certifying authority has its own system;
- there is a lack of electronic request systems in the certifying authorities and also no possibility of tracking the submitted requests;
- some authorities do not allow open discussions about the CPP requests, e.g. prior to a rejection of the CPP application, because of minor mistakes/clarifications;
- charging processes vary across certifying authorities which can lead to unnecessary delays in CPP issuance;
- there are inconsistencies in listing the trademark of the recipient country on the CPP if different from the certifying country;
- required legalizations lead to delays in CPP availability (see Section 3.Q8).

2. Related to issuing country

2.Q1 Does WHO issue CPP?
2.A1 No, WHO does not issue CPPs or any of the certificates described under the Scheme.

2.Q2 Can any one issue a CPP?
2.A2 No, only countries and regional organizations, such as the European Medicines Agency (EMA), that are party to the Scheme, can issue CPPs.

2.Q3 What should Member States and regional organizations possess in order to issue a CPP to support the export pharmaceutical products?
2.A3 Member States and regional organizations should have the following to issue a CPP:

- an effective national licensing system for pharmaceutical products, manufacturers and distributors;
- GMP requirements consonant with those recommended by WHO to which all manufacturers of FPPs are required to conform;
• effective controls to monitor the quality of pharmaceutical products registered or manufactured within the country, including access to an independent quality control laboratory;
• a national pharmaceutical inspectorate having the technical competence experience and resources to assess whether GMP and other controls are effectively implemented and legal power to conduct appropriate investigations;
• the administrative capacity to issue the required certificates, to institute inquiries in the case of complaint associated with a potentially serious quality defects or other hazard and to notify WHO and other concerned parties.

2.Q4 Should a CPP issued by Member States bear the WHO emblem or the acronym “WHO”?  
2.A4 No, certificates should not bear the WHO emblem or the acronym “WHO”. The use of the emblem or acronym creates the impression that the certificate is issued or endorsed by WHO. It is an illegal act and countries receiving such CPPs should reject them and report to WHO. The CPP should always appear on the certifying authority’s headed paper or emblem.

2.Q5 By whom is a CPP issued and for what requirement in the recipient authority?  
2.A5 A CPP is issued by the authorized body of the exporting country and is intended for use by the competent authority within an importing country:
• when a pharmaceutical product is under consideration for a product license/marketing authorization that will authorize its importation and sale in the importing country;
• when administrative action is required to renew, extend vary or review such license;
• it should be provided at the end of the review process for markets that also require the detailed dossier.

2.Q6 Is the CPP evidence of quality, safety, efficacy review and approval?  
2.A6 Yes, the CPP is based on the assumption that the authorities issuing a CPP have the capacity to assess the quality, safety and efficacy (QSE) of the product they approve for marketing. Based on the intention of the Scheme, a recipient authority could require a CPP when it does not undertake a full review of QSE data submitted for registration and evidence of approval in another country is required.

2.Q7 What is the significance of the declaration of marketing status, i.e. whether the product is actually on the market in the exporting country?  
2.A7 Declaration of marketing authorization approval is the aim of the CPP. It is true that the WHO format CPP includes information on marketing status (if the product is actually on the market of the certifying country) but the Scheme also has a provision where the certifying authority can indicate why the product may not be marketed. In circumstances where the product is not actually on the market the issuing authority can indicate that in the certificate. The actual presence on the market of the product depends on many other factors. The recipient authority should not require that a product be marketed in the certifying country. The focus of the CPP is to ensure that a full review has been undertaken by the authority to ensure QSE.
2.Q8 Imagine a situation in which a product is authorized for marketing in the country of manufacture, but is not actually available on the market. Can the competent authority of the exporting country issue a CPP to support export?

2.A8 Yes, it can issue a CPP. What it should do is explain why it is not on the market. One reason for not being on the market could be that the disease/health problem for which the product is indicated may not be prevalent in the country. For products approved according to Article 58 (Regulation (EC) No. 726–2004) for diseases/health problems in certain regions, the EMA only can issue the CPPs within the WHO format.

2.Q9 Sometimes a country may wish to import a special dosage form, strength or formulation of a certain known product, and this particular product may not be registered in the manufacturing country. Under such circumstances, can the authority of the exporting country issue a CPP?

2.A9 Yes, it can issue a CPP, but it should explain on the certificate:
- that the particular product is not authorized for marketing in the exporting country;
- that it has been produced based on the request of the importing country; and
- that the manufacturing is in compliance with GMP.

The export certificate may look different and have differences in format. However, there may be restrictions on this dependent on individual legislation in the exporting country.

3. Related to recipient country

3.Q1 When would a CPP be required?

3.A1 When the CPP replaces either a full or partial QSE review, the CPP would be a condition of approval and it would not be required at the time of submission. If local legislation stipulates provision of a CPP at the time of submission, the authority review should be a “verification” procedure with published, communicated timelines that should be short and thus not delaying patient access (see Section 1.Q16).

3.Q2 Is it a must that a pharmaceutical product has to be exported from the same country as the certifying authority?

3.A2 No, it is not necessary for the product to be exported from the certifying country as long as a declaration of GMP assurance appears on the CPP. The Scheme was established on the basis that the certifying country was also the country where finished product manufacture took place and was therefore the exporting country. Subsequent revisions to the Scheme have introduced scope for CPPs to be issued by other reference authorities. Most certifying authorities currently provide CPPs when the finished product is not manufactured in the certifying country on the basis that GMP is assured. Moreover many authorities assume that certifying authorities issue CPPs even when finished product manufacture does not occur in the certifying country. Strict adherence to the above assumption potentially limits licensing and registration options and can delay the introduction, or affect the continued supply, of important medicines.
3. Q3  Is it possible to obtain a CPP from a certifying authority that is not the country where the manufacture of the finished product takes place?
3.A3  Yes, the Scheme has a provision that when manufacture takes place in a country other than that where the product certificate is issued, an attestation that such manufacture complies with GMP may still be provided as an attachment to the product certificate, on the basis of inspections undertaken for registration purposes. The GMP declaration in the CPP will refer to assurance of GMP for the product approved in the certifying country at the stated site, even if the manufacturing site is in a different country than the issuing authority.

3. Q4  Is it necessary for the CPP to come from the country where finished product manufacture takes place?
3.A4  No, although the Scheme was set up assuming that the certifying country was also the country where finished product manufacture takes place, there is scope within the Scheme for CPPs to be issued by other authorities that can provide independent assurance of the GMP compliance status. There needs to be an appreciation of the complexity of manufacturing and sourcing routes currently employed by companies operating internationally. WHO Member States define the “source” differently:
• country of finished product manufacture;
• country of final packing;
• country of final release;
• country of main headquarters of the pharmaceutical company, etc.
The critical element is the confirmation that all production/manufacturing/quality operations are carried out according to GMP. Due to complex modern, sourcing routes, together with varying local regulatory processes, the approval in the country where finished product manufacture takes place may be later than in other countries. In this case it is a matter of judgment as to whether it is necessary for the CPP to be issued from the country where finished product manufacture takes place. The preference, in order to speed up patient access, would be to accept the CPP from the earlier approving country – in order to approve the product the certifying authority must also be assured of GMP. Implementation and compliance with GMP ensures quality of product irrespective of source. Requirement of an additional CPP for the release site if it is different from the product manufacture site, delays patient access since multiple CPPs provide no additional value.

3. Q5  Should recipient authorities require a CPP from more than one certifying authority?
3.A5  No, under most circumstances they should not require a CPP from more than one certifying authority. A WHO-format CPP from a single certifying authority should provide appropriate evidence of approval and GMP status. However, certain regulations may require provision of more than one CPP.

3. Q6  Business Process Scenario Questions for when a product is contract manufactured?
3.A6  Imagine a situation in which a company within Europe produces a pharmaceutical product, and the product is authorized for marketing in that European country. However,
the company also produces the product under contract manufacturing in a second
country, e.g. in Asia, and wants to export from there to Africa.
The authority of the importing country should receive the CPP from the European
country to prove quality efficacy and safety of the approved product.

Supporting questions:

3.Q6.1 Is contract manufacturing accepted?
3.A6.1 Yes, contract manufacturing is accepted under GMP.

3.Q6.2 In case of a contract-manufactured product: from which country should
the authority in the importing country (recipient authority) accept the
Certificate for a Pharmaceutical Product (CPP)?
3.A6.2 The country where the contract manufacture is taking place can issue a CPP
if the product is registered by the authority of that country. If the product is not
registered where the contract manufacture is taking place then the authority
cannot issue the CPP, but an export certificate (see Section 2, Q/A 9).
• If the contract-manufactured product is also authorized for marketing in the
  European country, then the European country can issue certificate.
• If the contract-manufactured product is also authorized by an additional
  stringent health authority, then this authority can issue a CPP.

3.Q7 Can a CPP also be used to provide evidence of an administrative review and
approval (e.g. as certification of acceptability of a company name change)?
3.A7 Yes, the CPP can also provide evidence of an administrative review and approval (e.g.
as certification of acceptability of a company name change:
• for a name change of the owner of a manufacturing or production site), which often
  happens in the context of company mergers and acquisitions;
• for administrative approvals that now involve a QSE review, recipient authorities
  should use alternatives to a CPP as a preferred and quicker option;
• issues related to manufacturing company name change (“administrative review”)
  may indeed create various practical difficulties for exporters–importers, but are
  not associated directly with safety/quality concerns and should be given less
  prominence).

3.Q8 Is it necessary to legalize the CPP?
3.A8 No, legalization is not part of the WHO Scheme and this is not considered to provide
additional assurance of authenticity. Approval statuses in key reference countries are
currently available as public information.
Legalization should not be necessary since an official governmental authority of the
certifying country signs the CPP.
Legalization does not add value to the CPP, as it confirms only the signatures on the
CPP but does not confirm any details of the CPP content.
Legalization delays availability of the CPP and therefore delays access to medicines
for patients. If a recipient authority has any doubts about the validity of a CPP it should
contact the certifying authority directly. In addition, cash payment required by certain
embassies could cause unnecessary delays to the CPP availability.
A number of recipient countries are no longer asking for legalization as long as the CPP
strictly follows the WHO format.
4. GMP status

4.Q1  Is it necessary for recipient authorities to require GMP certificates in addition to a CPP?
4.A1  No, the CPP includes a GMP declaration, so additional GMP certificate is not necessary.
   • Following the introduction of the WHO CPP some authorities no longer issue GMP certificates (e.g. US-FDA).
   • In the CPP context separate GMP certificates are redundant and are therefore discouraged. CPPs should be accepted (in particular from the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and International Conference on Harmonisation (ICH) regions) as evidence of GMP status.
   • Outside the Scheme, there are occasions when it is appropriate to require a GMP certificate.

4.Q2  Does the CPP provide evidence of GMP?
4.A2  Yes, the GMP declaration in the CPP refers to assurance of GMP for the product approved in the certifying country at the stated manufacturing site(s). In addition, CPPs issued by NMRAs party to the PIC/S and ICH regions (European Union, Japan and United States of America) provide evidence of GMP status. When a CPP is provided it is not necessary to provide additional GMPs for finished products.

4.Q3  What is the difference between approval of the quality data in the submission and evidence of GMP?
4.A3  The approval of the quality information in a submission is an approval of how the applicant company proposes to manufacture and control the quality of the product at the time of manufacture and throughout the product’s life. The evidence of GMP compliance shows, that the applicant company has been able to demonstrate that the manufacturing site fulfils the underlying GMP principles.

4.Q4  When a CPP forms part of a regulatory review, is it necessary to conduct a site inspection as well?
4.A4  An inspection should not be necessary when the GMP declaration on the CPP covers the product to be approved in the recipient country.
   • Inspections outside of this condition are a matter of judgment and decision by the recipient country. Membership of PIC/S, ICH or other means of recognizing inspections by other authorities is encouraged.
   • The acceptance of the GMP status in the CPP helps to reduce unnecessary inspections.
   • CPPs should be accepted (in particular from PIC/S and ICH regions) as evidence of MP status. The decision to inspect should be made after a risk-based assessment of the facility, taking into account GMP and inspection status from other authorities.

5. Alternatives to a CPP

5.Q1  Are there any alternatives to a CPP as evidence of approval by a national medicine regulatory authority (NMRA)?
5.A1  Outside the WHO Certification Scheme other forms of evidence include:
• product approval letters (or copies of licenses) from well-established NMRAs, e.g. Australia, Canada, People’s Republic of China, Denmark, Finland, Germany, India, Japan, Norway, Republic of Korea, Spain, United Kingdom, United States of America;
• positive scientific opinion from EMA;
• decisions of the European Commission;
• European public assessment report;
• licensing/approval information on regulatory authority websites and evidence of approval on the United States Food and Drug Administration website.

5.Q2 When and by whom is a statement of licensing status of pharmaceutical product(s) (SLSPP) issued?
5.A2 An SLSPP is issued by the competent authority of the exporting country and is intended for use by importing agents when considering bids in an international tender. It is requested by the importing agent as a condition for bidding. The SLSPP is not intended for use for regulatory submissions.

5.Q3 What is a batch certificate?
5.A3 A batch certificate is a certificate that accompanies and attests to the quality and expiry date of a specific batch or consignment that has already been licensed/approved for marketing in the importing country.
• A batch certificate is usually issued by the manufacturer.
• In case of biological products, a lot certificate is issued by the competent authority of the exporting country.

6. Glossary

Terms

Competent authority
A medicines regulatory authority which has the legally delegated or invested authority, capacity, or power to perform a designated function

Stringent authority
The same as competent authority, but related to a certain reputation and generally an authority of a developed market, such as the Food and Drug Administration, European Medicines Agency, Therapeutic Goods Administration, etc.

The following terms are used with the same meaning:

| Certifying/issuing country | These terms always refer to the competent authority – in most cases of a developed market which issues the CPP |
| Certifying/issuing (health) authority |  |
| Exporting country |  |
| Requesting country | These terms always refer to the emerging market which needs the CPP from a developed market, as stipulated in the regulatory requirements |
| Recipient country |  |
| Importing country |  |
Safety news

**Safety warnings**

**Warfarin: calciphylaxis**

*United Kingdom* – The MHRA has informed healthcare professionals about the conclusions of an EU-wide review which found that on rare occasions warfarin use might lead to calciphylaxis, including in patients with normal renal function. If calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping warfarin treatment.

Calciphylaxis, also known as calcific uraemic arteriolopathy, is a very rare but serious condition that causes vascular calcification and cutaneous necrosis. The mortality rate is high. The condition is most commonly observed in patients with known risk factors such as end-stage renal disease.

   PRAC recommendations on signals, EMA/PRAC/313187/2016. 26 May 2016.

**Eltrombopag: potentially fatal liver injury**

*Canada* – Health Canada has published a warning about the risk of severe liver toxicity associated with the systemic haemostatic medicine eltrombopag (Revolade®). This follows the identification of five cases fulfilling the criteria for severe drug-induced liver injury in a recent review of all clinical trial and post-marketing cases.

To mitigate the risk of severe hepatotoxicity and potentially fatal liver injury, healthcare professionals should: measure serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin before initiating eltrombopag, every two weeks during the dose adjustment phase, and then monthly following establishment of a stable dose. In patients with normal liver function, eltrombopag should be discontinued if ALT levels increase to $\geq 3 \times$ upper limit of normal (ULN). In patients with elevations in transaminases before treatment, eltrombopag should be stopped if ALT levels increase to $\geq 3 \times$ baseline or $> 5 \times$ ULN, whichever is the lower. The Canadian product monograph has been updated to reflect this new safety information. (1)

The risk of hepatotoxicity and precautions for use have also been included in the product information for eltrombopag approved in the EU. (2)

   (2) EMA Product information, Revolade -EMEA/H/C/001110 -IAIN/0034/G.

**Etonogestrel implants: migration from insertion site**

*United Kingdom* – The MHRA has issued a warning about rare reports of complications with etonogestrel (Nexplanon®) contraceptive implants. In rare cases, such implants have moved from the insertion site and reached the lung via the pulmonary artery. An implant that cannot be palpated at its insertion site in the arm should be located as soon as possible and removed at the
earliest opportunity. If an implant cannot be located within the arm, chest imaging should be performed. Correct subdermal insertion reduces the risk of these events.


**Ombitasvir/paritaprevir/ritonavir: acute renal failure**

**Japan** – Following reported cases of acute renal failure in patients treated with the hepatitis C medicine ombitasvir/paritaprevir/ritonavir (Viekirax®) in Japan, the Ministry of Health, Labour and Welfare (MHLW) has recommended updates to the product information to include the following advice: Before starting this drug and periodically during treatment, renal function tests should be performed. As renal function may suddenly deteriorate in particular in patients with decreased renal function and in patients concomitantly receiving calcium channel blockers, these patients should be carefully monitored. If any abnormalities are observed, the drug should be discontinued and appropriate measures should be adopted.


**Blinatumomab: pancreatitis**

**Canada** – Health Canada has informed health professionals about reported cases of life-threatening, sometimes fatal pancreatitis associated with the use of blinatumomab (Blincyto®) in clinical trial and post-market settings, and about new recommended precautions. The diagnosis of pancreatitis should be considered in patients treated with blinatumomab who experience severe upper abdominal pain accompanied with nausea, vomiting or abdominal tenderness. If pancreatitis is suspected, blinatumomab should be either temporarily interrupted or discontinued.

Blinotumumab is a monoclonal antibody approved in Canada for the treatment of adult patients with certain forms of relapsed or refractory acute lymphoblastic leukaemia. The Canadian product information has been updated to reflect this new safety information.

Health Canada Advisory, 13 July 2016.

**Carmustine intracerebral implant: risk of air accumulation**

**Japan** – The PMDA has informed health professionals that in patients receiving a carmustine (Gliadel®) intracerebral implant, air accumulation may occur at the implant site, and there have been reports of neurological symptoms. Accordingly, the Ministry of Health, Labour and Welfare (MHLW) has recommended updates to the product information for carmustine. After the implantation patients should be monitored for neurological symptoms, such as hemiplegia, aphasia, and disturbed consciousness, and appropriate measures adopted if any abnormalities are observed.

PMDA Summary of investigation results and MHLW Revisions of precautions, 5 July 2016.

**Idelalisib: updated measures to manage risk of infections**

**European Union** – The EMA has completed its review of idelalisib (Zydelig®), confirming that its benefits outweigh its risks in the treatment of two types of blood cancers, chronic lymphocytic leukaemia (CLL) and follicular lymphoma. Updated recommendations have been provided to manage the risk of serious infections which was also
confirmed by the review. All patients treated with idelalisib should be given antibiotics to prevent *Pneumocystis jirovecii* pneumonia during treatment and for up to 2 to 6 months thereafter. Patients should be monitored for infection and white blood cell counts should be performed regularly. Idelalisib should not be started in patients with a generalized infection.

A precautionary recommendation had initially been issued, advising against starting idelalisib treatment in patients with previously untreated CLL whose cancer cells have certain genetic mutations. The updated advice now allows initiation of idelalisib in these patients, provided that there are no alternative treatment options and that the recommended measures to prevent infection are followed.

► **EMA Press release, 22 July 2016.**

### Opioids and benzodiazepines: potentially fatal side effects

**United States of America** – An extensive FDA review has found that the growing combined use of opioid medicines with benzodiazepines or other central nervous system (CNS) depressants has resulted in serious side effects, including slowed or difficult breathing and deaths. A boxed warning and revisions to the *Warnings and Precautions, Drug Interactions,* and *Patient Counseling Information* sections have been included in the product information for opioid and benzodiazepine medicines class-wide.

Opioid pain medicines should only be prescribed together with benzodiazepines or other CNS depressants if alternative treatment options are inadequate. In such cases, the lowest possible dosage and duration of each drug should be used to achieve the desired clinical effect. Health professionals should warn patients and caregivers about the risks of slowed or difficult breathing and/or sedation and the associated signs and symptoms.

The use of opioid cough medicines should be avoided in patients taking benzodiazepines or other CNS depressants, including alcohol.

► **FDA Drug safety communication, 31 August 2016.**

**FDA News release, 31 August 2016.**

### Levetiracetam: acute renal failure

**Japan** – Revisions to the approved product information have been recommended for the anti-epileptic medicine levetiracetam (Keppra®) in Japan to warn about the risk of acute renal failure. This follows reported cases of acute kidney failure in patients treated with levetiracetam in Japan. Revised product information recommends that patients should be carefully monitored and that if any abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be adopted.

► **MHLW Pharmaceuticals and Medical Devices Safety Information No. 334, May 2016 [English translation issued on 28 June 2016]. Pages 23-24.**

### Citalopram: suspected drug interaction with cocaine

**United Kingdom** – The MHRA has advised health professionals to enquire about possible nonmedical drug use before prescribing medicines that have the potential to interact adversely with illicit drugs. This follows the death of a man from subarachnoid haemorrhage that raised concerns about a suspected drug interaction between the antidepressant
citalopram and cocaine. An expert group advised that hypertension related to cocaine and an additive increased bleeding risk in combination with citalopram could be plausible mechanisms for such an interaction.

Health professionals were also reminded of potential interactions between cocaine and selective serotonin reuptake inhibitors (SSRIs), and of the need to avoid concurrent use of multiple serotonergic drugs.


Restrictions

Riociguat: not for patients with pulmonary hypertension caused by idiopathic interstitial pneumonia

European Union, Canada – The EMA and Health Canada have reminded health professionals that the antihypertensive medicine riociguat (Adempas®) should not be used in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonia. A contraindication will be added to the product information to help ensure that the medicine is not used in this patient population.

The recommendation follows the early termination of a phase II clinical trial called RISE-IIP which was investigating the effects of the medicine in these patients. Preliminary results showed an increased number of deaths and serious adverse events, with no clinically significant benefit.

   MHRA Drug Safety Update volume 10 issue 1, August 2016: 1.

Fluoroquinolones: use only in certain serious infections

United States of America – The FDA has approved labelling changes to limit the use of fluoroquinolones in acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary tract infections to patients that have no other treatment options. This follows a warning communicated in May 2016 about the risk of disabling and potentially permanent serious side effects that can occur, including tendon inflammation and rupture, peripheral neuropathy, psychiatric reactions, photosensitivity, and prolongation of QTc interval. The benefits of fluoroquinolones continue to outweigh their risks in certain serious bacterial infections such as anthrax, plague and bacterial pneumonia.

► FDA News release, 26 July 2016.
   FDA Drug safety communication, 26 July 2016.

Known risks

Canagliflozin, dapagliflozin: kidney injury

United States of America – The FDA has strengthened its warnings about the risk of acute kidney injury associated with the type 2 diabetes medicines canagliflozin (Invokana®, Invokamet®) and dapagliflozin (Farxiga®, Xigduo XR®). Health professionals should consider individual risk factors for kidney injury and should assess kidney function before starting canagliflozin or dapagliflozin therapy. Kidney function should be monitored periodically thereafter. If acute kidney injury occurs, the medicine should
be discontinued promptly and the kidney impairment treated.

► [FDA Drug safety communication, 15 June 2016](#).

**Apixaban: Liver function disorder**

Japan – The Pharmaceuticals and Medical Devices Agency (PMDA) has informed health professionals that cases of liver function disorder have been reported in Japan in patients treated with the anti-thrombotic agent apixaban (Eliquis®). Based on these findings, the Ministry of Health, Labour and Welfare (MHLW) has recommended changes to the product information stating that hepatic function disorder associated with increased levels of AST (GOT), ALT (GPT) and other findings in liver function tests may occur, and that patients should be carefully monitored. If any abnormalities are observed, administration of apixaban should be discontinued and appropriate measures should be taken. (1)

Elevation of liver transaminases are also listed as adverse reactions in the product information for apixaban approved in the European Union. (2)

► (1) [PMDA Summary of investigation results and MHLW Revisions of precautions, 5 July 2016](#).

(2) [EMA. Eliquis : EPAR - Product Information. Last updated 15 April 2016](#).

**Clarification of indications**

**Fingolimod: not proven in progressive multiple sclerosis**

Japan – The PMDA has recommended updates to the product information for fingolimod (Gilenya®) to clarify the precautions concerning its indications. The product is approved in Japan to prevent relapse and to delay accumulation of physical disability in multiple sclerosis. Wording has been added to the product information stating that fingolimod did not slow progression of physical disability in an overseas placebo-controlled study in patients with primary progressive multiple sclerosis, and providing an overview of the findings and a reference to the published study.

► [PMDA Report on the investigation results, 23 June 2016](#).

**Medical device-related**

**Blood clotting time measuring devices: inaccurate readings**

Canada – Alere Inc. has withdrawn the Alere INRatio® and INRatio®2 Prothrombin Time Monitoring Systems (professional and self-test) devices from the Canadian market. These devices measure blood clotting time in patients requiring warfarin and other oral blood-thinning medicines.

There is a risk that the devices provide an inaccurate low reading. This could result in an improper dosage of warfarin or other blood-thinning medications being administered, leading to excessive bleeding with potentially serious adverse outcomes.

► [Health Canada Advisory, 16 July 2016 and 22 July 2016](#).

[Health Canada Advisory, 16 July 2016](#).

[TGA Alert, 21 July 2016](#).

**N-acetylcysteine and biochemistry assays**

United Kingdom – The MHRA has advised health professionals who are treating patients with N-acetylcysteine for paracetamol overdose to establish whether Siemens ADVIA Chemistry and
Dimension/Dimension Vista instruments are used for laboratory testing of biochemistry. If so, they should do venipuncture and blood sampling before N-acetylcysteine administration, as there is a risk of false low biochemistry test results if blood is sampled during or immediately after administration. When requesting biochemistry tests (such as cholesterol, uric acid, lactate) that include any affected assays from these instruments, health professionals should state that a patient is receiving N-acetylcysteine.

- Drug Safety Update volume 9 issue 12, July 2016: 3.
- MHRA Medical safety alert, 22 June 2016 (includes a full list of affected assays).

# Medicines safety reviews started

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| Retinoid medicines (acitretin, adapalene, alitretinoin, bexarotene, isotretinoin, tazarotene and tretinoin) | Treatment of skin conditions, including acne and psoriasis. Some retinoids are used to treat certain forms of cancer. | Need to evaluate current measures for pregnancy prevention and for minimizing the possible risk of neuropsychiatric disorders. | As above
  See also: Health Canada Advisory, 7 September 2016. |
Non-compliance with good practices

This section provides an overview of recent warnings and alerts issued as a result of inspection findings. Increasingly, such findings have led to concerns about data integrity. The reasons are diverse and include the increased use of computerized systems in pharmaceutical development and manufacturing, improved capacities of inspectors, and a lack of awareness among manufacturers of the significance of data integrity and regulatory expectations (1).

This has prompted the development of new regulatory guidance on data integrity, including finalized EMA guidance (see page 401), draft FDA guidance (2) and draft MHRA guidance (see page 404). In 2015, WHO issued a new guidance text – the first international text – on good data and record management practices (3).

It consolidates the normative principles into one comprehensive document and gives detailed examples of how they can be implemented. In delivering the 2016 MHRA annual lecture, the WHO Director-General thanked international experts who contributed to this guidance, saying that it will “help reduce incidents of incomplete presentation of data by manufacturers or deliberate data falsification” (4).

(1) WHO Essential medicines and health products news, 3 June 2016.

Alkem Laboratories Ltd, India: data integrity issues

European Union – The EMA concluded its review of medicines for which studies have been conducted by Alkem Laboratories Ltd, and has announced that bioequivalence studies conducted at the Alkem site in Taloja, India, cannot be used to support marketing authorization in the EU. A riluzole-containing product has been suspended, and an ibuprofen-containing product will be refused authorization until alternative data are presented from other sources. For three other antibiotic products – two authorized products and one under evaluation – alternative bioequivalence data have been provided.

The recommendations follow a joint routine inspection by German and Dutch authorities in March 2015, which revealed misrepresentation of data in two different trials performed in 2013 and 2014 at the Taloja site. The findings cast doubts on the quality management system in place at the site, and thus on the reliability of the data of bioequivalence studies conducted between March 2013 and March 2015.


Quest Life Sciences Pvt Ltd, India: data integrity issues

United Kingdom – The MHRA has suspended the marketing authorization of a generic erythromycin product that had been approved based on clinical trials conducted by India’s Quest Life Sciences. This follows an MHRA inspection of the Quest Life Sciences site in February 2016, which revealed several data integrity issues. Four other pending applications for marketing authorization that rely on studies conducted by Quest Life Sciences may be rejected. This affects products
containing doxycycline, cephalexin and metformin. (1)

The WHO Prequalification Team (PQT) had issued a notice of concern to Quest Life Sciences in July 2015. (2)

► (1) UK drugs regulator halts approvals for Indian clinical trials firm. Reuters, 1 July 2016.
(2) WHO Prequalification update, 3 July 2015.

Semler Research Centre Pvt Ltd, India: EMA review concluded

European Union – The EMA has concluded its review of Semler Research Centre Private Ltd, Bangalore, India, and has recommended suspending a number of nationally approved medicines for which bioequivalence studies were conducted at Semler. National authorities can postpone the suspension for medicines of critical importance. Furthermore, medicines still under evaluation cannot be granted authorization in the EU on the basis of studies conducted at Semler. (1)

The review followed an FDA inspection that identified several issues at Semler’s bioanalytical site, including the substitution and manipulation of subjects’ clinical samples. The FDA had notified pharmaceutical companies that studies conducted at Semler are unacceptable to support approval of medicines (2).

The WHO Prequalification Team had also raised serious concerns regarding data integrity and manipulation of study samples following its own inspections of Semler’s bioanalytical and clinical sites. A WHO Notice of Concern was issued to Semler in April 2016 (3).

► (1) EMA Press release, 22 July 2016.
(2) FDA Notification to pharmaceutical companies, 20 April 2016.
(3) WHO Notice of Concern, 12 April 2016.

Zhejiang Medicine Co Ltd, China: unreported impurity testing results

United States of America – The FDA has issued a warning letter to Zhejiang Medicine Co. Ltd as a follow-up to observations made an inspection of its Xinchang Pharmaceutical Factory in June 2015. The investigators had found chromatograms from unofficial testing, showing large unknown peaks of uncharacterized impurities, including potential contaminants, in the active pharmaceutical ingredients (APIs) tested. These results were not reported in the official records for the API samples. In addition, worksheets were found to have been backdated, and actions were not traceable to specific individuals due to failures in the company’s data integrity systems. The company was requested to conduct a comprehensive investigation into the extent of the failures and a risk assessment of their potential effects.

In August 2016, the FDA Center for Drug Evaluation and Research also issued warning letters to the API manufacturer Unimark Remedies Ltd, India over similar deficiencies (2), the finished product manufacturer Huzhou Aupower Sanitary Commodity Co., Ltd, Zhejiang, China (3), the API manufacturer Xinxiang Tuoxin Biochemical Co. Ltd, Henan, China (4), and the finished product manufacturers Pan Drugs Ltd, Vadodara, India (5), and Lima & Pergher Industria e Comercio S/A, Minas Gerais, Brazil (6). All FDA warning letters are available on the Agency’s website (7).

► (1) FDA Warning letter, 4 August 2016.
(2) FDA Warning letter, 12 August 2016.
(3) FDA Warning letter, 10 August 2016.
(4) FDA Warning Letter, 19 August 2016.
(7) www.fda.gov/ICECI/EnforcementActions/WarningLetters/
Pharmaceutics International Inc., U.S.: non-compliance with GMP

European Union – The EMA has started a review of medicines manufactured by Pharmaceutics International Inc., USA, following several shortcomings observed in good manufacturing practice (GMP) inspections conducted by the MHRA in June 2015 and February 2016. The shortcomings included insufficient measures to reduce the risk of cross-contamination, as well as deficiencies in data management and quality assurance systems.

Pharmaceutics International Inc. manufactures sodium phenylbutyrate (Ammonaps®), which is centrally authorized in the EU, and a number of nationally authorized medicines.


Shanghai Desano Co Ltd, China: non-compliance with GMP

United States of America – The FDA has issued a warning letter to the active pharmaceutical ingredients (API) manufacturer Shanghai Desano Chemical Pharmaceutical Co Ltd following findings on non-compliance with good manufacturing practices (GMP) during an inspection conducted at the site in Laogang Town, Pudong District, in May 2015. No import alert has been issued by the FDA. (1)

In response to the issuance of the FDA warning letter, the WHO Prequalification Team has requested manufacturers of prequalified products that use API manufactured by Shanghai Desano to take additional measures such as comprehensive testing upon receipt, to help ensure that the quality of all API batches is assured. (2)

► (1) FDA Warning letter, 16 June 2016.
   (2) WHO PQT Information note, 5 July 2016.

Laxachem Organics Pvt Ltd, India: import ban for refusal of inspection

United States of America – The FDA has issued an import alert for products from Laxachem Organics Pvt. Ltd., Ahmednagar, Maharashtra, India, because the company has refused to allow FDA investigators to inspect its facility. Laxachem manufactures active pharmaceutical ingredient (API) for repackers, labelers and wholesale drug distributors.

According to the company’s website, one of the APIs supplied by Laxachem is docusate sodium. A voluntary nationwide recall of oral liquid docusate sodium from a domestic manufacturer had been organized in the United States in July due to contamination with Burkholderia cepacia, a bacteria linked to an outbreak in five U.S. states. This was followed by a voluntary recall of all liquid products by that manufacturer.

► FDA Update, 15 August 2016.
Falsified medicines

Falsified quinine sulphate circulating in West and Central Africa

Geneva – WHO has issued a Medical Product Alert relating to the recent circulation of two confirmed falsified versions of quinine sulphate circulating in Cameroon and the Democratic Republic of the Congo, containing zero active pharmaceutical ingredient.

Quinine sulphate is used for the treatment of *P. falciparum* malaria in the region.

The products were first discovered by a local non-governmental organization. They failed field screening and were submitted to a WHO-prequalified quality control laboratory. Subsequent analysis showed that neither product contained any of the stated active pharmaceutical ingredient.

Details of the products are shown below.

<table>
<thead>
<tr>
<th>Product discovered in Cameroon:</th>
<th>Product discovered in Bunia, Dem. Rep. of the Congo:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product name: Quinine Sulfate 300 mg</td>
<td>Quinine Sulphate 300mg</td>
</tr>
<tr>
<td>Number of tablets per container: 1000 tablets</td>
<td>100 tablets</td>
</tr>
<tr>
<td>Batch number: 10H05</td>
<td>F4387</td>
</tr>
<tr>
<td>Expiry Date: 09/2018</td>
<td>11/18</td>
</tr>
<tr>
<td>Date of manufacture: 09/2014</td>
<td>12/14</td>
</tr>
<tr>
<td>Stated manufacturer: Novadina Pharmaceutical Ltd, London, United Kingdom</td>
<td>CAD Pharm, India</td>
</tr>
</tbody>
</table>

WHO requests increased vigilance within the supply chains of countries likely to be affected by these falsified products. Increased vigilance should include hospitals, clinics, health centres, pharmacies and any other suppliers of medical products. Health authorities are asked to immediately notify WHO if these falsified products are discovered in their country. Any information on their supply and/or distribution should be sent to rapidalert@who.int.

► WHO Medical Product Alert No. 4/2016 (includes photographs).
Regulatory news

Pre-market assessment

EMA report on adaptive pathways pilot

European Union – The EMA has published a final report on the experience gained during its pilot project on adaptive pathways. The pilot was launched in March 2014 and has now ended. The adaptive pathways approach makes use of existing regulatory tools to address unmet medical needs. A medicine will first be authorized in a small patient population that is likely to benefit most from it. Additional evidence is then gathered over time resulting in progressive licensing adaptations to extend or restrict the previously authorized indications.

Of 62 applications received during the pilot, 18 led to meetings with stakeholders, and seven of these progressed to receive further advice through the adaptive licensing route. The pilot has shown that adaptive pathways can bring multiple stakeholders together to agree on a plan to generate data on a medicine across its lifespan, particularly in areas where evidence generation is challenging. Aspects for further reflection have been identified. A stakeholder workshop on the adaptive pathways approach will be held on 8 December 2016.

Medicines developers are invited to submit proposals for adaptive licensing to the EMA. An updated guidance document has been published on the Agency’s website, outlining the steps to follow.

► EMA Press release, 3 August 2016.

Experiences in publishing assessment reports

A joint article published in Drug Discovery Today describes the positive experiences of the EMA and the TGA with the publication of assessment reports for medicines. According to the authors, increasing web traffic highlights the regulators’ success in facilitating access to information on medicines and how they are evaluated. The article concludes that European public assessment reports (EPARs) and Australian Public Assessment Reports (AusPARs) ensure high transparency about the reasons for marketing authorization of medicines, and that regulatory authorities can learn from each other when making information on medicines publicly available.


Collaboration

EMA and FDA collaborate on patient engagement

European Union, United States of America – The EMA and the FDA have set up a new working group to exchange best practices on how to involve patients in development, evaluation and post-authorization activities related to medicines.

Patients bring real-life experience as well as specific knowledge and expertise
to regulatory discussions on medicines. Their involvement is a priority for both agencies. The new cluster is expected to meet three to four times per year via teleconference. Areas for discussion will include the processes for selecting and preparing patients to take part in the agencies’ activities, ensuring that patients are independent and representative, and reporting on the impact of patient involvement.


Post-market surveillance

New EMA guidance on monitoring of biological medicines

European Union – The EMA has published a number of finalized guidance texts on its EU Good Pharmacovigilance Practices (EU-GVP) web site, including a new chapter titled Product- or population-specific considerations II: Biological medicinal products. The chapter provides guidance on how to better monitor and manage the safety of biological medicines to optimize the safe and effective use of these products in Europe.

Biological medicines contain one or more active substances made by or derived from a biological source, such as blood or plasma. The active substances of biological medicines are larger and more complex than those of non-biological medicines. The new guidance takes into account the complexity of biological medicines and their inherent variability in molecules of the same active substance, particularly in different batches of a medicine. It highlights specific issues and challenges for the pharmacovigilance of biological medicines, e.g. in relation to variability of the active substance or traceability of products, provides recommendations on how to address these specificities and challenges, and outlines the roles and responsibilities of the various actors.

The new chapter comes into force on 16 August 2016. It applies to biological medicines, biosimilars and medicines which contain the same or a closely related active substance but are not authorized as biosimilars. It does not apply to vaccines or advanced therapy medicinal products, as separate guidance already exists for these.

The EU-GVP is a key deliverable of the 2010 pharmacovigilance legislation. It applies to centrally authorized and nationally authorized medicines. An updated module on post-authorization safety studies has also been released, giving clearer guidance for these studies and distinguishing between legal obligations and recommendations. In addition, EU-GVP draft texts on management and reporting of adverse reactions, signal management and signal detection have been published for comment.


EMA. Good pharmacovigilance practices [web site]. Updated 15 August 2016.

Report on pharmacovigilance activities in Europe

European Union – The European Commission has published a report on the pharmacovigilance activities of the European medicines regulatory network in the three years following the introduction of the new pharmacovigilance legislation in July 2012.

The creation of the Pharmacovigilance Risk Assessment Committee (PRAC) and the regulatory tools made available under the revised legislation have enabled
faster detection of safety issues. Some of the concrete achievements during the past three years include the use of risk management plans as an integral part of proactive safety management, improved reporting of side-effects with an increase by 50% in direct reports from patients, investigation of safety signals by the PRAC and prompt regulatory actions where needed, submission of periodic safety update reports (PSURs) by pharmaceutical companies for assessment of the benefit-risk balance of marketed medicines by regulators, and safety-related referrals leading to PRAC recommendations for a harmonized position across the EU.

► EMA News, 8 August 2016.

**Good manufacturing practice**

**EMA adopts data integrity guidelines**

European Union – The EMA has released new good manufacturing practice (GMP) guidance to ensure the integrity of data generated in the process of testing, manufacturing, packaging, distribution and monitoring of medicines. Regulators rely on these data to evaluate the quality, safety and efficacy of medicines and to monitor their benefit-risk profile throughout their life span.

Data integrity is key to public health protection. Controlling of data records helps ensure that the data generated are accurate and consistent to support good decision-making by both pharmaceutical manufacturers and regulatory authorities. The advice, which applies to both paper-based and electronic systems, is aligned with existing GMP guidance published by some regulatory authorities participating in the Pharmaceutical Inspection Co-operation Scheme (PIC/S). It should be read in conjunction with national guidance, medicines legislation and the GMP standards published in Eudralex volume 4.


**Labelling**

**Improved product labels in Canada**

Canada – Health Canada has released new guidance for industry on improved labels and packages that will minimize the risk of confusion. Two “Good Label and Package Practices” guides have been provided, one for over-the-counter medicines and another for prescription drugs. The guidance includes instructions for a new standardized Facts Table that will be required on the outer labels of over-the-counter drugs, with easy-to-read product information such as ingredients, directions and warnings. The requirement will be phased in from June 2017.


**Antibiotics**

**EMA recommends reducing veterinary use of colistin**

European Union – The EMA has recommended that countries should reduce the use of the last-resort antibiotic colistin in animals to decrease the risk of antimicrobial resistance. The goal is to cut colistin sales by 65%. Colistin-containing medicines should only be used as a second line treatment in animals. In addition, colistin should be reclassified into the category of antimicrobials listed by WHO as critically important to human health.
The advice updates EMA guidance from 2013 and takes into account comments made by stakeholders during a public consultation that ended on 26 June 2016. The European Commission requested this update in response to the discovery of a new mechanism of colistin resistance caused by the mcr-1 gene, which can be transferred between different types of bacteria. The gene was first identified in *Enterobacteriaceae* in South China, and has also been found in the EU and other regions.


Global implications of antibiotics control in India

India – Following the recent ban of around 330 fixed-dose combinations (FDCs) by the Government of India, including 63 products containing antibiotics, the authors of an article in *The Lancet Global Health* have urged the international community to support the full implementation of the ban, emphasizing that controlling antibiotic resistance in India is key for controlling antibiotic resistance worldwide.

Growing worldwide trade and travel has allowed resistant microorganisms to spread rapidly. New Delhi metallo-β-lactamase, an enzyme that causes bacteria to be resistant to antibiotics, was first reported in India in 2008 and is now found worldwide. Some of the banned FDCs have reportedly been exported to African and Asian countries.


Tripartite meeting on evaluation of new antibacterial agents

London – At a meeting held between the regulatory authorities of Europe, Japan and the United States on 1-2 September 2016, the three agencies discussed regulatory approaches that could stimulate the development of new antibiotics to fight antimicrobial resistance and protect global public health. They agreed that alignment of data requirements for the evaluation of new antibacterial agents can support this aim, but that some flexibility is needed where treatment options are limited due to antimicrobial resistance, and that abbreviated clinical development programmes for new antibiotics may be appropriate to address unmet needs related to antimicrobial resistance. They also identified areas of closer collaboration and coordination of efforts to encourage the development of safe and effective antibacterial treatments.

The next tripartite meeting is scheduled to take place in spring 2017.


Controlled substances

Tighter control of W-18 in Canada

Canada – The Government of Canada has published final amendments to add the synthetic, potentially harmful substance W-18 to Schedule I of the Controlled Drugs and Substances Act (CDSA) and to the Restricted Drugs section of the Food and Drug Regulations, making unauthorized activities such as production, possession, importation or exportation and trafficking illegal. There is evidence that W-18 has been used recreationally in Europe and Canada. W-18 has been found in samples falsely
labelled as legitimate medicines such as oxycodone that were seized by Canadian law enforcement authorities in 2015. (1)

Health Canada has clarified that the tightened controls were adopted in view of data published in the patent application for W-18 showing its very high activity against pain on mice, suggesting a potentially severe risk for harm. In the absence of data on the use of W-18 in humans there is no specific knowledge on its mechanisms of action, its pharmacology, or whether naloxone would be effective to reverse its effects. (2)

(2) Health Canada advisory, 13 June 2016.

Canada proposes scheduling of fentanyl precursors
Canada – Health Canada has proposed to move forward with plans to restrict six chemicals used in the production of fentanyl, to make their unauthorized importation and exportation illegal. This follows an increase in domestic production of illicit fentanyl reported by the Canadian police.

The proposed regulatory change is part of Health Canada’s opioid action plan, which was announced by the Health Minister in June 2016.


Blood safety

Shorter deferral period for MSM in Canada
Canada – Health Canada has authorized two Canadian blood operators to reduce the deferral period for blood donation for men who have sex with men (MSM) from five years to one year. The two operators had submitted scientific data which were reviewed by Health Canada and found to support the conclusion that the change would not reduce the safety to recipients of donated blood.

This change brings Canada into line with several other countries which have implemented a one-year deferral period for men who have sex with men, including the United States, Australia, New Zealand, England, Scotland and France.


All U.S. blood donations to be screened for Zika virus
United States of America – As a further safety measure against the emerging Zika virus outbreak, the FDA has issued a revised guidance recommending universal testing of donated whole blood and blood components for Zika virus in the U.S. and its territories. In earlier guidance, screening had been recommended only in areas with active Zika virus transmission. The expanded testing will reduce the risk of Zika virus transmission.

► FDA News release, 26 August 2016.
**Under discussion**

**United Kingdom** – The MHRA has published draft data integrity guidance for industry. The guidance covers data governance systems across good practices related to the laboratory, clinical, manufacturing, distribution and pharmacovigilance areas. It addresses fundamental failures identified in regulatory inspections. The deadline for comments is 31 October 2016.  
► MHRA Announcement, 21 July 2016.

**European Union** – The EMA has published draft guidance on the use of innovative modelling and simulation in medicines development. The draft guideline gives detailed advice on the data that should be included in a modelling report of an application dossier, and the supportive data needed to assess a modelling platform. Comments are invited until 31 January 2017.  
► EMA News, 29 July 2016.

**European Union** – The EMA has launched a public consultation on revised guidance regarding the development of medicines to treat tuberculosis. The guidance is an addendum to EMA’s guideline on the evaluation of medicines to treat bacterial infections. Comments can be sent to the Agency until 31 January 2017.  
► EMA News, 1 August 2016.

**European Union** – Updated guidance texts on the management and reporting of adverse reactions, signal management and signal detection have been published for comment on the EMA good pharmacovigilance practices (GVP) website. The deadline for comment is 18 October 2016.  
► EMA. Good pharmacovigilance practices [web site]. Updated 15 August 2016.

**United States of America** – The FDA has published two draft guidance texts on next generation sequencing (NGS) diagnostics, a new technology to scan human DNA to detect genomic variations that may point to individual health risks or help to inform treatment decisions. Public comments are invited during a 90-day comment period.  
► FDA News release, 6 July 2016.

**United States of America** – The FDA has established a public docket and requested comments regarding options for blood donor deferral policies to reduce the risk of HIV transmission. Specifically, comments are invited on the feasibility of moving from the existing time-based deferrals to alternate options such as the use of individual risk assessment. The comment period is 120 days.  
Approved

**Lixisenatide for type 2 diabetes**
- **Product name**: Adlyxin®
- **Dosage form**: Once-daily injection
- **Class**: Glucagon-like peptide-1 (GLP-1) receptor agonist; **ATC code**: A10BX10
- **Approval**: FDA
- **Use**: Treatment of adults with type 2 diabetes.
- **Benefits**: Improvement of haemoglobin A1c levels.
- **Safety information**:
  - Severe hypersensitivity reactions, including anaphylaxis, were reported in clinical trials.
  - The FDA has required post-market studies on immunogenicity and on safety and efficacy in children.
  - Lixisenatide should not be used to treat people with type 1 diabetes or patients with diabetic ketoacidosis.
- ► [FDA News release, 28 July 2016](#).

**Cholera vaccine**
- **Product name**: Vaxchora®
- **Dosage form**: Oral liquid
- **Class**: Live, attenuated cholera vaccine; **ATC code**: J07AE02
- **Approval**: FDA (fast-track designation, priority review)
- **Use**: Prevention of cholera in travellers.
- **Benefits**: Additional cholera-prevention measure for travellers.
- ► [FDA News release, 10 June 2016](#).

**Lifitegrast for dry eye disease**
- **Product name**: Xiidra®
- **Dosage form**: Ophthalmic solution
- **Class**: Lymphocyte function-associated antigen 1 (LFA-1) antagonist
- **Approval**: FDA
- **Use**: Treatment of dry eye disease.
- **Benefits**: Improvement in signs and symptoms of eye dryness.
- **Safety information**: The safety and efficacy of lifitegrast in patients below the age of 17 years has not been studied.
- ► [FDA News release, 12 July 2016](#).

**Cell-based therapy to support stem cell transplant in blood cancer patients**
- **Product name**: Zalmoxis®
- **Dosage form**: Dispersion for infusion
- **Class**: Genetically modified allogeneic T cells
- **Approval**: EMA (conditional approval; orphan designation)
- **Use**: Add-on treatment in haploidentical haematopoietic stem cell transplantation of adult patients with high-risk haematological malignancies.
- **Benefits**: Ability to increase overall survival rates.
- **Safety information**: This product can cause graft-versus-host disease. A suicide gene in the modified T cells makes them susceptible to ganciclovir or valganciclovir. One of these medicines can therefore be given to prevent further development of the disease.
- ► [EMA Press release, 24 June 2016](#).

**Biosimilar**

**Etanercept-szzs**
- **Product name**: Erelzi®
- **Dosage form**: Injection
- **Biosimilar to**: Enbrel® (etanercept)
- **Approval**: FDA (approved as a biosimilar, not as an interchangeable product)
- **Use**: Treatment of multiple inflammatory diseases.
- **Safety information**: Etanercept-szzs should not be given to patients with sepsis.
- ► [FDA News release, 30 August 2016](#).
Extensions of indications

**Emtricitabine & tenofovir disoproxil for HIV pre-exposure prophylaxis**

**Product name:** Truvada®

**Approval:** EMA recommendation

**Newly approved use:** In combination with safer sex practices, to reduce the risk of sexually-acquired human immunodeficiency virus type 1 (HIV-1) infection in adults at high risk.

**Note:** This indication was approved to enable intensification of preventive measures against HIV, given the high number of new infections worldwide.


**Cabozantib, lenvatinib approved in the EU for kidney cancer**

**Product name:** Cabometyx® (cabozantib), Kisplyx® (lenvatinib)

**Approval:** EMA recommendation (accelerated assessment)

**Newly approved use:** Treatment of advanced renal cell cancer (in the case of lenvatinib: in combination with everolimus)

**Note:** The two medicines were previously approved for thyroid cancer both in the EU and in the U.S. under the names of Cometriq® (cabozantib) and Lenvima® (lenvatinib). In the U.S., their indications were extended in April and May 2016 respectively to include advanced renal cancer.


Interim import approval

**Naloxone nasal spray to prevent deaths from opioid overdose**

Canada – The Canadian Minister of Health has signed an Interim Order to temporarily allow naloxone in nasal spray form to be imported from the U.S. and sold in Canada. Until now, only the injectable format of naloxone was available in Canada.

Naloxone nasal spray is under expedited review for authorization in Canada. The import order was granted to enable immediate access to easy-to-use formats of naloxone by police and family members, to help prevent deaths from opioid overdoses. An English and French instruction sheet will be provided together with the product.


Diagnostics

**Assay to detect markers for antibiotic resistance**

**Product name:** Xpert Carba-R® Assay

**Approval:** FDA

**Use:** Detection of specific genetic markers associated with carbapenemase, the enzyme produced by Carbapenem-resistant *Enterobacteriaceae*, in patient specimens. The test is intended to be used in conjunction with other clinical and laboratory findings.

**Benefits:** Testing of specimens from patients enables faster detection of resistance markers than testing of samples derived from bacterial cultures.

**Note:** The Xpert Carba-R® Assay tests only for genetic material. It does not detect bacteria, carbapenemase activity or other possible non-enzymatic causes of carbapenem resistance. Neither does it detect all types of carbapenemase genes. It is important to recover bacteria for accurate tracking of the spread of carbapenem resistance. Laboratories should continue to perform standard bacterial culture in conjunction with the use of the Xpert Carba-R® Assay. In addition, concomitant cultures are necessary to recover organisms for epidemiological typing, antimicrobial susceptibility testing and confirmatory bacterial identification.

► FDA News release, 29 June 2016.
Publications and events

Access to medicines

UNHRC resolution on access to medicines

Geneva – The UN Human Rights Council (UNHRC) has adopted by consensus a resolution on access to medicines that reaffirms the right of everyone to the enjoyment of the highest attainable standard of physical and mental health.

The resolution urges all States, the WHO and relevant organizations to promote innovative research and development to address health needs in developing countries, including access to quality, safe, efficacious and affordable medicines, taking into account the WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property. It further calls on member states to make full use of the flexibilities provided by the agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and to continue collaborating, “as appropriate, on models and approaches that support the delinkage of the cost of new research and development from the prices of medicines, vaccines and diagnostics for diseases that predominantly affect developing countries”. A panel discussion will be held in March 2017 on best practices and challenges in access to medicines.

► Intellectual Property Watch news, 1 July 2016.

WHO to convene stakeholders on fair medicines pricing

Geneva – In an online commentary the WHO Assistant Director-General for Health Systems and Innovation, Dr Marie-Paule Kieny, has announced that WHO is planning to convene governments, patient groups and industry stakeholders to develop a fair pricing model that can affordably deliver the medicines needed by patients.

As some new medicines are unaffordable even for wealthy countries, and some older medicines are in great shortage, new approaches are needed to reach universal health coverage, which is at the centre of global health efforts under the Sustainable Development Goals. Dr Kieny proposed that, for this objective to be reached by 2030, the public and private spheres should enter into a social contract, enabling innovation and generic production to respond effectively to global public health needs by providing, quality, safe, effective treatments which are both available and affordable.

► WHO Media Centre. Commentary by Marie-Paule Kieny, Assistant Director-General, Health Systems and Innovation. 5 July 2016.

New book on intellectual property rules and access to medicines

Amsterdam – A book and web site launched by Health Action International (HAI) describe the impact of the patent system on access to medicines and encourage governments to use available legal flexibilities to safeguard access to
needed treatment. The web site provides information about the relationship between intellectual property and access to medicines as well as more in-depth analyses into key issues, along with resources and infographics.

► HAI Press release, 13 July 2016.

**Medicines Patent Pool signs new licences**

*Geneva* – The Medicines Patent Pool (MPP) has announced new generic manufacturing licences for four antiretrovirals – lopinavir/ritonavir, atazanavir and raltegravir – as well as the direct-acting antiviral daclatasvir to treat hepatitis C. The MPP has signed licences with Aurobindo, Desano, Emcure, Hetero Labs, Laurus Labs, Lupin and new partner Zydus Cadila for a total of nine new agreements to produce generic versions of key WHO-priority treatments for HIV and hepatitis C.


**Hepatitis C patent landscape**

*Geneva* – WHO has published updated patent information for seven new hepatitis C medicines which are included in the WHO List of Essential Medicines: sofosbuvir, ledipasvir, daclatasvir, simeprevir, paritaprevir, ombitasvir and dasabuvir. The reports cover more than 40 countries, territories and regions and provide clarity on whether or not the medicines are patent-protected in individual countries. This knowledge is important for governments in making treatment available to their populations.

► WHO Public health, innovation, intellectual property and trade. WHO updates patent information on treatments for Hepatitis C [web page].

**Insulin patent landscape**

A new publication in the *Journal of Pharmaceutical Policy and Practice* provides an overview of the patent landscape for insulin. The authors conclude that the global market dominance of expensive analog over human insulins, offered by a few manufacturers, will likely continue even though many patents for insulin analogs will expire soon. A way forward would be to find generic manufacturers that will offer acceptable off-patent human insulin products for export. (1)

The paper is one in a series produced under the ACCISS Project, a multi-year effort to understand what is causing the barriers to insulin access and to address the inequities in the global market. (2)


(2) Health Action International. ACCISS study [web site]. http://haiweb.org/what-we-do/acciss/

**Pharmacovigilance**

**Two new CIOMS publications**

*Geneva* – The Council for International Organizations of Medical Sciences (CIOMS) has released two new publications for health professionals involved in safety surveillance of medicines.

The publication *Evidence Synthesis and Meta-Analysis for Drug Safety, Report of CIOMS Working Group X* is for readers who are interested in analysis of drug safety data or meta-analysis more generally. It provides the rationale for
why and when a meta-analysis should be considered in the context of regulatory decision-making, and describes the tasks, data collection, and analyses that need to be carried out to inform those decisions. While most guidance and reviews in this area give more attention to assessment of pre-defined benefits, this report focuses on combining evidence on harms that emerge in the post-market setting.

The book titled Development and Rational Use of Standardised MedDRA Queries (SMQs): Retrieving Adverse Drug Reactions with MedDRA – Second Edition is useful for those wishing to search databases on Individual Case Safety Reports (ICSRs) coded according to the MedDRA® system. It provides examples of standardized queries that are relevant in different contexts such as systematic analyses, interventional clinical trials, signal detection or safety signal assessment.

CIOMS is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949. Its publications are available directly from CIOMS (www.cioms.ch) or from the WHO bookshop (http://apps.who.int/bookorders/).


**Disease updates**

**Polio virus: public health emergency of international concern**

Geneva – At the advice of the Emergency Committee under the International Health Regulations (2005) (IHR), the WHO Director-General has declared the continuation of the public health emergency of international concern with regard to the spread of both wild poliovirus and circulating vaccine-derived poliovirus.

Temporary recommendations will remain in place for countries that are infected by, vulnerable to, and/or exporting the two types of virus.

The Committee was gravely concerned about information indicating that wild poliovirus had been circulating undetected in Nigeria for several years and would likely spread to Cameroon, Chad and Niger, as well as the deteriorating security in parts of Afghanistan which may delay efforts for polio eradication.

► WHO Statement, 22 August 2016.

**Zika: public health emergency continues**

Geneva – Based on the advice provided by the Emergency Committee under the International Health Regulations (2005) at its third and fourth meetings (1, 2), the WHO Director-General has declared the continuation of the Public Health Emergency of International Concern posed by Zika virus infection and has reaffirmed the existing recommendations for public health measures. At the time of the fourth Committee meeting, there were no reports of confirmed cases of Zika virus among people who attended the Games. The Committee reaffirmed its previous advice that there should be no general restrictions on travel and trade with areas with Zika virus transmission, including the cities in Brazil that will be hosting the Paralympic Games. Acknowledging that the impact of Zika virus is a long term concern, the Committee recommended focus on several new research issues. It further recommended that the Director-General should consider developing an appropriate infrastructure and response plan within WHO.

WHO, the Pan American Health Organization (PAHO) and partners have
set out their strategic response to Zika. A greater focus will be placed on preventing and managing medical complications, information and counselling services, and integrated vector control measures. Implementation of the strategic response plan from July 2016 to December 2017 will cost US$ 122 million. (3)

► (1) WHO Statement, 14 June 2016.
   (2) WHO Statement, 3 September 2016.
   (3) WHO Note for the media, 17 June 2016.

Sexually transmitted infections: new WHO treatment guidelines

Some antibiotics are failing in the treatment of these STIs as a result of misuse and overuse. Without effective treatment, complications can result that can cause serious illness and sometimes death. The new recommendations are based on the latest available evidence. For gonorrhoea, the new WHO guidelines recommend against the use of quinolones due to widespread high levels of resistance. For syphilis, the new WHO guideline strongly recommends a single dose of benzathine penicillin given by injection, instead of oral antibiotics. WHO is working with partners to help address prevailing shortages of benzathine penicillin.

WHO is calling on countries to update their national treatment guidelines and to start using the updated recommendations immediately.


Non-communicable diseases: uneven progress
Geneva – A new WHO report highlights the need to intensify national action to meet the global targets to protect people from heart disease, cancers, diabetes, and lung diseases. Globally, these four noncommunicable diseases (NCDs) remain the leading causes of mortality. The sustainable development goals include a goal to reduce, by one third, the premature mortality from NCDs in people aged under 70 years.

The findings of a global 2015 survey show that a number of countries have adopted measures to prevent tobacco use, harmful use of alcohol, unhealthy diet, and physical inactivity. However, progress is insufficient and uneven.

► WHO Note for the media, 18 July 2016.


Hepatitis B and C: need for more access to testing and treatment
Geneva – WHO has urged countries to increase access to hepatitis testing and treatment and to step up preventive strategies. This follows the adoption, at the 2016 World Health Assembly, of the first ever Global Health Sector Strategy and global targets to fight viral hepatitis. The Second World Hepatitis Summit will take place in Brazil in March 2017.

Globally, 400 million people are infected with hepatitis B and C, more than 10 times the number of people living with HIV. Only one in 20 people with viral hepatitis is diagnosed with the disease, and only one in 100 is being treated.

Direct-acting antivirals can cure more than 90% of patients within 2-3 months. While their high costs continue to put
treatment out of most people’s reach, prices are declining especially in countries that have access to generics. For example, in Egypt the cost of a hepatitis C treatment course dropped from US$ 900 in 2014 to less than US$ 200 in 2016.


HIV

Key challenges
Durban – At the International AIDS Conference in Durban, South Africa, WHO has flagged four key challenges to the global HIV response. Firstly, the number of new infections has remained high, and renewed attention must be paid to prevention, for example by exploiting new interventions such as pre-exposure prophylaxis (PrEP). Secondly, while WHO has recommended that all people diagnosed with HIV start antiretroviral therapy (ART) as soon as possible, there is a need for more ready access to simple and affordable testing services and for tailored treatment programmes to reach all those in need. Thirdly, vigilance and quick action are required to minimize the emergence of drug resistance, and lastly, there is a need for sustainable financing of the global response. (1)

HIV and injectable contraceptives
Geneva – WHO will convene an expert review group later in 2016 to examine the links between the use of various hormonal contraceptive methods and women’s risk of HIV acquisition. The expert review group will assess whether current WHO guidance needs to change in light of the findings of a WHO-commissioned systematic review, published in AIDS on 9 August 2016 (2).

While the data continue to indicate no association with risk of HIV acquisition for oral contraceptive pills, injectable norethisterone enantheate and levonorgestrel implants, they strengthen existing concerns about a possible increase in risk of HIV acquisition in women using injectable depot medroxyprogesterone acetate. (3)

► (1) WHO Note for the media, 15 July 2016.

Vaccines

Yellow fever emergency vaccination campaigns
Geneva – The Emergency Committee under the International Health Regulations (2005) determined that the current status of the yellow fever outbreaks in Angola and the Democratic Republic of the Congo (DRC) does not constitute a Public Health Emergency of International Concern (PHEIC) at this time, but requires sustained scaled up response activities and close monitoring. (1)

In the last two weeks of August 2016, more than 7.7 million people in Kinshasa and a further 1.5 million people in DRC’s border regions with Angola were vaccinated in an emergency campaign accomplished through an extraordinary network of partnerships and collaborations. The campaign built on previous emergency campaigns led by national governments, which had reached more than 13 million people in Angola.
and more than 3 million in DRC since the beginning of the outbreak in December 2015 (2).

To achieve maximum population coverage the recent campaign used the ‘fractional dosing’ approach recommended by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization, whereby one fifth of the regular dose of yellow fever vaccine can confer immunity for at least 12 months (3). Full doses were given to pregnant women and infants, who may have a weaker immune response. A USAID-funded study will evaluate the immune response achieved during the campaign.

The International Health Regulations still require a full dose for travellers. A 2014 amendment entered into force in July 2016 under which all countries recognize that a single full dose confers life-long immunity.

WHO has prequalified yellow fever vaccines from four different vaccine manufacturers which together produce an annual volume of around 80-90 million doses. A global stockpile of 6 million doses is funded by Gavi, the Vaccine Alliance, The stockpile was depleted twice between February and June 2016 due to the need to control outbreaks. (3)

► (1) WHO Statement, 31 August 2016.
(2) WHO News release, 2 September 2016.
(3) WHO Statement, 17 June 2016.

Global vaccine quality control laboratories networking meeting
Lage Vuursche, Netherlands – At a meeting hosted jointly by WHO and the Dutch National Institute for Public Health and the Environment (RIVM) from 30 August to 2 September 2016, participants from 22 countries agreed to establish a global network of control laboratories performing lot release of WHO-prequalified vaccines.

Lot release by regulatory authorities is an important element in the regulation of vaccines. It serves to confirm that each batch of a vaccine meets the specifications of the product as laid down in the approved marketing authorization.

WHO-prequalified vaccines are used to immunize 65% of infants worldwide. The proposed network – the first at the global level – is intended as a platform for participating laboratories to share information in order to strengthen mechanisms for reliance and work-sharing and promote harmonization of testing. This is expected to result in more effective and streamlined processes both for regulators and for manufacturers, thus increasing global access to WHO-prequalified vaccines at affordable costs.

► WHO Immunization standards. WHO-RIVM Global Vaccine Quality Control Laboratories Networking Meeting [web page].

WHO matters

New WHO guideline welcomed
The Hague, Netherlands – New guidelines have been released jointly by WHO and the International Pharmaceutical Federation (FIP) on providing medicines for children when no authorized product exists.

Health professionals all over the world have long struggled with the lack of authorized and commercially available child-specific medicines. They are often forced to use adult medicines when treating children for example by crushing tablets, or to make products from scratch. These approaches pose a certain risk of inaccurate dosing and can impact on the quality, safety and efficacy of the
medicine. The new guidance provides advice based on available evidence, best practices and sound scientific and therapeutic principles, and provides practical examples.


FIP-WHO technical guidelines: Points to consider in the provision by health care professionals of children-specific preparations that are not available as authorized products.

WHO Prequalification Team offers GMP pre-inspections

Geneva – To assist manufacturers in resource-limited countries who are keen to attain product prequalification, the WHO Prequalification Team (PQT) is initiating a pilot collaboration enabling manufacturers to request verification of their compliance with the principles of good manufacturing practice (GMP) even before they have submitted an application for WHO prequalification.

The concept of this approach has been tested successfully in cooperation with the Nigeria’s National Agency for Food and Drug Administration (NAFDAC) and the Pharmaceutical Manufacturers Association of Nigeria (PMG-MAN).

► PQ Update, 17 June 2016.

MQAS Finished pharmaceutical product questionnaire posted

Geneva – WHO has posted a Word version of the Interagency Finished Product Questionnaire (1) on its web site, for ease of use by manufacturers and other parties.

The Interagency FPP questionnaire is an appendix to the WHO Model Quality Assurance System (MQAS) for procurement agencies (2). It is the common format to be used by manufacturers to submit product data to international organizations. Such data are reviewed for those needed medicines of which no WHO-prequalified or stringently authorized products are available.

The WHO MQAS was updated in 2014 in collaboration with the Interagency pharmaceutical working group, which brings together the major organizations involved in international procurement of medicines.

► (1) WHO MQAS Appendix 6 - Interagency finished pharmaceutical product questionnaire based on the model quality assurance system for procurement agencies. Available at:

WHO. Essential medicines and health products. Guidelines. – Distribution


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

Chlorhexidine digluconate solution
(Chlorhexidini digluconatis solutio)

This is a draft proposal for The International Pharmacopoeia (Working document QAS/16.668, June 2016). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

\[
\text{C}_{22}\text{H}_{30}\text{Cl}_2\text{N}_{10}\text{O}_{7}\text{C}_{6}\text{H}_{12}\text{O}_7
\]

Relative molecular mass. 897.8

Chemical name. 1,1’-(hexane-1,6-diyl)bis[5-(4-chlorophenyl)biguanide] di-D-gluconate, 2,4,11,13-tetraazatetradecanediimide, N,N’-bis(4-chlorophenyl)-3,12-diamo-, di-D-gluconate; CAS Reg. No. 18472-51-0.

Description. Chlorhexidine digluconate is an aqueous solution of chlorhexidine digluconate. It is a clear, colourless or pale yellow liquid.

Miscibility. Miscible with water, with not more than 3 parts of acetone R and with not more than 5 parts of ethanol (~750 g/L) TS.

Category. Antiseptic.

Storage. Chlorhexidine digluconate should be kept in a well-closed container (avoid unlined steel containers), protected from light.
Requirements

Chlorhexidine digluconate solution contains not less than 190 g per L and not more than 210 g per L of $C_{22}H_{30}Cl_2N_{10.2}C_6H_{12}O_7$.

Identity tests

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

A. To 1 mL of the solution add 40 mL of water R, cool in iced water, make alkaline to titan yellow paper R by adding dropwise, and with stirring, sodium hydroxide (~420 g/L) TS and add 1 mL in excess. Filter, wash the precipitate with water R until the washings are free from alkali. Recrystallize from methanol R. Dry the crystals at 100–105°C. 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 chlorhexidine RS or with the reference spectrum of chlorhexidine. If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and chlorhexidine RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from chlorhexidine RS.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica R5 as the coating substance and a mixture of 10 volumes of ammonia (~260 g/L) TS, 10 volumes of ethyl acetate R, 30 volumes of water R and 50 volumes of ethanol (~750 g/L) TS as the mobile phase. Apply separately to the plate 5 μL of each of the following 2 solutions in water R. For solution (A) dilute 10 mL of the preparation to be examined to a final volume of 50 mL. For solution (B) use 25 mg of calcium gluconate R per mL. After removing the plate from the chromatographic chamber dry the plate at 100°C for 20 minutes and allow to cool. Spray the plate with a solution containing 25 g/L ammonium molybdate R and 10 g/L ceric sulfate R in sulfuric acid (~98 g/L) TS. Heat the plate for about 10 minutes at 110°C. Examine the chromatogram in daylight. The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).

C. Dissolve 1 mL of the solution in 10 mL of water and add, with shaking, 0.15 mL of copper (II) chloride/ammonia TS; a purple precipitate is produced immediately. Continue to add 0.5 mL of copper(II)chloride/ammonia TS; the colour of the precipitate changes to blue.

D. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under "Related substances". The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (3).

pH value (1.13). Dilute 1 mL to 20 mL in carbon-dioxide-free water R, 5.5–7.0.

Relative density (1.3). $d_{20}^{20} = 1.06 – 1.07$.

Impurity P ($\rho$-Chloroaniline)

Prepare sample solution (A) by diluting 0.20 g of the test solution to 30 mL with water R. Add rapidly and with thorough mixing after each addition: 5 mL of hydrochloric acid (~103 g/L) TS, 0.35 mL of sodium nitrite (100 g/L) TS, 2 mL of ammonium sulfamate (50 g/L) TS, 5 mL of $N$-(1-naphthyl) ethylenediamine hydrochloride (1 g/L) TS and 1 mL of ethanol (~750 g/L) TS. Transfer this solution quantitatively to a 50.0 mL volumetric flask, dilute to volume with water R and allow to stand for 30 minutes.
Prepare reference solutions (B)–(F) representing respectively 0.005% (m/v), 0.01% (m/v), 0.02% (m/v) and 0.06% (m/v) of chloroaniline in the test sample as follows: Dilute 1.0 mL, 2.0 mL, 4.0 mL, 10.0 mL and 12.0 mL of a solution containing 10 μg per mL of chloroaniline R in hydrochloric acid (200 g/L) TS to 20 mL with water R. Then add 10.0 mL of water R. Add rapidly and with thorough mixing after each addition: 5 mL of hydrochloric acid (~103 g/L) TS, 0.35 mL of sodium nitrite (100 g/L) TS, 2 mL of ammonium sulfamate (50 g/L) TS, 5 mL of N-(1-naphthyl) ethylenediamine hydrochloride (1 g/L) TS and 1 mL of ethanol (~750 g/L) TS. Transfer each solution quantitatively to a 50.0 mL volumetric flask, dilute to volume with water R and allow to stand for 30 minutes.

Measure the absorbance (1.6) of solutions (A)–(F) in a 1 cm layer at the maximum at about 556 nm. Plot a calibration curve for solutions (B)–(F). Determine the concentration of chloroaniline from the calibration curve.

The content of p-chloroaniline is not more than 0.05% (m/v), calculated with reference to chlorhexidine gluconate solution.

Related substances

Prepare fresh solutions and perform the tests without delay.

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm). Maintain the column at 30°C.

Use the following conditions for gradient solution:

Mobile phase A: Mix 20 volumes of a 0.1% (v/v) solution of trifluoroacetic acid R in acetonitrile R and 80 volumes of a 0.1% (v/v) solution of trifluoroacetic acid R in water R;

Mobile phase B: Mix 10 volumes of a 0.1% (v/v) solution of trifluoroacetic acid R in water R and 90 volumes of a 0.1% (v/v) solution of trifluoroacetic acid R in acetonitrile R.

Use the following 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>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>100</td>
<td>0</td>
<td>Isocratic</td>
</tr>
<tr>
<td>2–32</td>
<td>100 to 80</td>
<td>0 to 20</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>32–37</td>
<td>80</td>
<td>20</td>
<td>Isocratic</td>
</tr>
<tr>
<td>37–47</td>
<td>80 to 70</td>
<td>20 to 30</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>47–54</td>
<td>70</td>
<td>30</td>
<td>Isocratic</td>
</tr>
<tr>
<td>54–56</td>
<td>70 to 100</td>
<td>30 to 0</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>56–66</td>
<td>100</td>
<td>0</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Prepare the following solutions in mobile phase A: For solution (1) transfer 1.0 mL of the preparation to be examined to a 100 mL volumetric flask and dilute to volume. For solution (2) transfer 1.0 mL of solution (1) to a 100 mL volumetric flask and dilute to volume. For
solution (3) dissolve the contents of a vial of chlorhexidine for system suitability RS (containing impurities A, B, F, G, H, I, J, K, L, N and O) in 1.0 mL.

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

Inject alternately 10 µL each of solutions (1), (2) and (3).

Use the chromatogram supplied with chlorhexidine for system suitability RS and the chromatogram obtained with solution (3) to identify the peaks due to impurities A, B, F, G, H, I, J, K, L, N and O.

Relative retention With reference to chlorhexidine (retention time = about 35 min):
impurity L = about 0.23; impurity Q = about 0.24; impurity G = about 0.25;
impurity N = about 0.35; impurity B = about 0.36; impurity F = about 0.5;
impurity A = about 0.6; impurity H = about 0.85; impurity O = about 0.90;
impurity I = about 0.91; impurity J = about 0.96; and impurity K = about 1.4.

The test is not valid unless in the chromatogram obtained with solution (3):
• the resolution between the peaks due to impurities L and G is at least 3.0;
• the peak-to-valley ratio (Hp/Hv) is at least 2.0, where Hp = height above the baseline of the peak due to impurity B and Hv = the height above the baseline of the lowest point of the curve separating this peak from that due to impurity N.

In the chromatogram obtained with solution (1):
• the area of any peak corresponding to impurity N is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);
• the area of any peak corresponding to impurity H is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);
• the areas of any peak corresponding to either impurities A, J or K is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);
• the sum of the areas of any peaks corresponding to impurities I and O is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);
• the area of any peak corresponding to impurity G is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);
• the areas of any peak corresponding to either impurities B, F, L or O is not greater than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);
• the areas of any peak corresponding to either impurities A, J or K is not greater than 0.4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);
• the area of any other impurity peak is not greater than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.10%);
• the sum of the areas of all impurity peaks is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%). Disregard any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Assay. Determine the weight per mL (1.3.1) of the preparation to be examined. Transfer about 1 g, accurately weighed, to a 250 mL beaker and add 50 mL of anhydrous acetic acid R. Titrate with 0.1 M 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 22.44 mg of C₃₄H₅₄Cl₂N₁₀O₁₄. 417
Impurities

A. 1-(4-chlorophenyl)-5-[6-[(cyanocarbamimidoyl)amino]hexyl]biguanide,

B. 1-[[6-[[[(4-chlorophenyl)carbamimidoyl]carbamimidoyl]amino]hexyl]carbamimidoyl]urea,

E. 1-(4-chlorophenyl)guanidine,

F. 1-(4-chlorophenyl)urea,

G. 1-(6-aminohexyl)-5-(4-chlorophenyl)biguanide,

H. 1,1’-[iminobis(carbamimidoyliminohexane-6,1-diyl)]bis[5-(4-chlorophenyl)biguanide],
I. unknown structure,

J. 1-(4-chlorophenyl)-5-[6-[[4-[(4-chlorophenyl)amino]-6-[(1S,2R,3R,4R,5S,6S)-1,2,3,4,5-pentahydroxypentyl]-1,3,5-triazin-2-yl]amino]hexyl]biguanide,


L. (5R,6S)-2-[[4-chlorophenyl]amino]-5-hydroxy-6-[(1R,2R)-1,2,3-trihydroxypropyl]-5,6-dihydro-4H-1,3-oxazin-4-one,

M. 5-(4-chlorophenyl)-5′-phenyl-1,1′-(hexane-1,6-diyl)biguanide,
N. 1-[6-(carbamimidoylamino)hexyl]-5-(4-chlorophenyl)biguanide,

O. 5-(2-chlorophenyl)-5′-(4-chlorophenyl)-1,1′-(hexane-1,6-diyl)dibiguanide,

P. 4-chloroaniline,

Q. unknown structure.

Reference substances to be established
chlorhexidine for system suitability RS

Reagents to be added to Reagents, test solutions and volumetric solutions

Sodium hydroxide (~420 g/L) TS.
A solution of sodium hydroxide R containing about 420 g/L of NaOH.

Titan yellow paper R
Impregnate filter paper with titan yellow TS. Allow to dry at room temperature.

Sulfuric acid (~98 g/L) TS.
Procedure. Add 55 mL of sulfuric acid (~1760 g/L) TS to sufficient water to produce 1000 mL; \( d \approx 1.063 \).

Hydrochloric acid (~103 g/L) TS
Hydrochloric acid (~420 g/L) TS, dilute with water to contain 103 g of HCl in 1000 mL.

Hydrochloric acid (~200 g/L) TS
Hydrochloric acid (~420 g/L) TS, dilute with water to contain 200 g of HCl in 1000 mL.

***
Chlorhexidine digluconate topical solution
(Chlorhexidini digluconatis solutio topicales)

This is a draft proposal for The International Pharmacopoeia (Working document QAS/16.669, June 2016). The working document with line numbers is available for comment at www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/. Please address any comments to: World Health Organization, Quality Assurance and Safety: Medicines, Dr Herbert Schmidt, 1211 Geneva 27, Switzerland; fax: +41 22 791 4730; email: schmidth@who.int.

Category. Antiseptic.

Storage. Chlorhexidine digluconate topical solution should be kept in a well-closed container, protected from light.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML): 5% (digluconate) and 7.1% (digluconate), delivering 4% chlorhexidine (for umbilical cord care); strengths in the current EML for children: 5% (digluconate) and 7.1% (digluconate), delivering 4% chlorhexidine (for umbilical cord care).

Definition. Chlorhexidine digluconate topical solution is a solution of Chlorhexidine digluconate solution in a suitable vehicle. It contains not less than 90.0% and not more than 110.0% of the amount of chlorhexidine digluconate \( \text{C}_{22}\text{H}_{30}\text{Cl}_2\text{N}_{10} \cdot 2\text{C}_6\text{H}_{12}\text{O}_7 \) stated on the label.

Identity tests
A. 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 50 volumes of dehydrated ethanol R, 10 volumes of ethyl acetate R, 10 volumes of ammonia (~260 g/L) TS R and 30 volumes of water R as the mobile phase. Apply separately to the plate 2 μL of each of the following 2 solutions in water R. For solution (A) dilute a quantity of the topical solution to obtain a solution containing 20 mg of chlorhexidine digluconate per mL. For solution (B) use a solution containing 10 mg of potassium gluconate R per mL. After removing the plate from the chromatographic chamber heat the plate for 20 minutes at 110°C and allow the plate to cool. Spray with ammonium molybdate/ceric sulfate/sulfuric acid TS. Heat the plate for 10 minutes at 110°C. Examine the chromatogram in daylight.

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

B. Transfer a quantity of the topical solution containing 5 mg of chlorhexidine digluconate into a 500 mL volumetric flask and dilute to volume with water R. The absorption spectrum (1.6) of the resulting solution, when observed between 200 nm and 320 nm, exhibits two maxima at about 231 nm and 255 nm, and two minima at about 218 nm and 242 nm.

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

pH value (1.13). 5.0–7.0.
Impurity P (4-Chloroaniline)

Prepare fresh solutions and perform the tests without delay. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the same chromatographic conditions as described under “Assay”.

Prepare the following solutions in mobile phase A:

For solution (1) transfer an amount of the topical solution, equivalent to 40.0 mg chlorhexidine digluconate to a 100 mL volumetric flask, and dilute to volume.

For solution (2) use 1.0 μg of 4-chloroaniline R per mL.

For solution (3) prepare a solution that contains 50 μg per mL of chlorhexidine diacetate RS and 1 μg per mL 4-chloroaniline R.

Inject 50 μL of solution (3) In the chromatogram obtained with solution (3) the peak due to 4-chloroaniline is eluted at a relative retention of about 1.3 with reference to chlorhexidine (retention time about 6 minutes). The test is not valid unless the resolution between the peaks due to 4-chloroaniline and chlorhexidine is at least 3.0.

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

Measure the areas of the peaks corresponding to 4-chloroaniline obtained in the chromatograms of solutions (1) and (2).

In the chromatogram obtained with solution (1):

• the area of any peak corresponding to 4-chloroaniline is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.05% (m/v) with reference to the concentration of chlorhexidine digluconate in the topical solution).

Assay

Prepare fresh solutions and perform the tests without delay.

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecysilane groups (5 μm).\footnote{Symmetry C18, 250 mm x 4.6 mm – 5 μm was found suitable.}

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>
</tr>
</thead>
<tbody>
<tr>
<td>0–9</td>
<td>100</td>
<td>0</td>
<td>Isocratic</td>
</tr>
<tr>
<td>9–10</td>
<td>100 to 45</td>
<td>0 to 55</td>
<td>Linear gradient</td>
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<td>10–15</td>
<td>45</td>
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<td>Isocratic</td>
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<tr>
<td>16–21</td>
<td>100</td>
<td>0</td>
<td>Isocratic</td>
</tr>
</tbody>
</table>

1 Symmetry C18, 250 mm x 4.6 mm – 5 μm was found suitable.
Operate with a flow rate of 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 239 nm.

Maintain the column temperature at 40°C.

Prepare the following solutions:

For solution (1) transfer an amount of the topical solution, equivalent to about 40 mg chlorhexidine digluconate, accurately weighed, to a 100 mL volumetric flask, and dilute to volume with methanol R. Further dilute a 10 mL portion of this solution with mobile phase A to 50 mL.

For solution (2) use 50 μg of chlorhexidine diacetate RS per mL in mobile phase A.

For solution (3) prepare a solution that contains 50 μg per mL of chlorhexidine diacetate RS and 1 μg per mL 4-chloroaniline R in mobile phase A.

Inject 50 μL of solution (3).

In the chromatogram obtained with solution (3) the peak due to 4-chloroaniline is eluted at a relative retention of about 1.3 with reference to chlorhexidine (retention time about 6 minutes). The assay is not valid unless the resolution between the peaks due to 4-chloroaniline and chlorhexidine is at least 3.0.

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

Measure the areas of the peaks corresponding to chlorhexidine obtained in the chromatograms of solutions (1) and (2). Determine the weight per mL (1.3.1) and calculate the percentage content of chlorhexidine digluconate, weight in volume, in the topical solution using the declared content of chlorhexidine in chlorhexidine diacetate RS \((\text{C}_{22}\text{H}_{30}\text{Cl}_{2}\text{N}_{10}\cdot 2\text{C}_{2}\text{H}_{4}\text{O}_{2})\). Each mg of chlorhexidine \((\text{C}_{22}\text{H}_{30}\text{Cl}_{2}\text{N}_{10})\) is equivalent to 1.776 mg of chlorhexidine digluconate \((\text{C}_{22}\text{H}_{30}\text{Cl}_{2}\text{N}_{10}\cdot 2\text{C}_{6}\text{H}_{12}\text{O}_{7})\).

**Impurities.** The impurity limited by the requirements of this monograph is impurity P listed in the monograph for Chlorhexidine digluconate solution.

**Reagents to be added to Reagents, test solutions and volumetric solutions**

Potassium gluconate R
\(\text{C}_{6}\text{H}_{11}\text{KO}_{7}\)

**Reference substances to be established**

Chlorhexidine diacetate RS
4-chloroaniline RS

***
Medroxyprogesterone acetate

(\textit{Medroxyprogesteroni acetas})

This is a draft proposal of a revised monograph for \textit{The International Pharmacopoeia} (Working document QAS/16.647, June 2016).

The working document with line numbers and tracked changes is available for comment at \url{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.

[\textbf{Note from the Secretariat.} Following information received from our custodian centre for International Chemical Reference Substances (ICRS), the European Directorate for the Quality of Medicines & HealthCare, it is proposed to revise the monograph on Medroxyprogesterone acetate.]

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

\begin{center}
\begin{picture}(400,200)
\put(0,0){\includegraphics[width=0.5\textwidth]{medroxyprogesterone_acetate estructura.png}}
\end{picture}
\end{center}

\begin{itemize}
\item C_{24}H_{34}O_{4}
\end{itemize}

\textbf{Relative molecular mass.} 386.5

\textbf{Chemical name.} 6\alpha\text{-methyl}-3,20-dioxopregn-4-en-17-yl acetate; (6\alpha)-17-(acetyloxy)-6-methylpregn-4-ene-3,20-dione; 17-hydroxy-6\alpha\text{-methylprogesterone acetate; CAS Reg. No. 71-58-9.}

\textbf{Description.} A white or almost white, crystalline powder.

\textbf{Solubility.} Practically insoluble in water; soluble in acetone R and dioxan R; slightly soluble in ethanol (~750 g/L) TS, methanol R and ether R.

\textbf{Category.} Progestogen.

\textbf{Storage.} Medroxyprogesterone acetate should be kept in a tight container, protected from light.

\textbf{Requirements}

\textbf{Definition.} Medroxyprogesterone acetate contains not less than 97.0% and not more than the equivalent of 103.0% of C_{24}H_{34}O_{4}, calculated with reference to the dried substance.

\textbf{Identity tests}

\begin{itemize}
\item Either test A or tests B and C may be applied.
\end{itemize}
A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from medroxyprogesterone acetate RS or with the reference spectrum of medroxyprogesterone acetate.

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

B.1 Carry out the test as described under 1.14.1 Thin-layer chromatography using silica R5 as the coating substance and a mixture of 10 volumes of dichloromethane R and 1 volume of ethyl acetate R as the mobile phase. Apply separately to the plate 10 μL of each of the following three solutions in dichloromethane R. For solution (A) use 2.5 mg of Medroxyprogesterone acetate per mL. For solution (B) use 2.5 mg of medroxyprogesterone acetate RS per mL. After removing the plate from the chromatographic chamber heat it at 120°C for 30 minutes, spray with 4-toluenesulfonic acid/ethanol TS and heat further at 120°C for 10 minutes. Allow the plate to cool and examine the chromatogram in ultraviolet light (365 nm).

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

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described under test B.1, but spray the plate with a mixture of equal volumes of sulfuric acid R and ethanol (~750 g/L) TS and heat further at 120°C for 10 minutes. Allow the plate to cool and examine the chromatogram in daylight.

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

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

Specific optical rotation. Use a 10 mg/mL solution in acetone R; [a]20°C = +47° to +53°.

Sulfated ash. Not more than 1.0 mg/g.

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

Impurity F

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

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

For solution (1) dissolve 20 mg of Medroxyprogesterone acetate in 5.0 mL of acetonitrile R and dilute to 10.0 mL with water R. For solution (2) dilute 0.5 volume of solution (1) to 100 volumes with the mobile phase. For solution (3) use 0.2 mg of medroxyprogesterone acetate RS and 0.01 mg of medroxyprogesterone acetate impurity F RS per mL mobile phase.

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

Inject 25 μL of solution (1), (2) and (3). In the chromatogram obtained with solution (3) impurity F is eluted at a relative retention of about 1.8 with reference to medroxyprogesterone acetate (retention time about 8 minutes).
In the chromatogram obtained with solution (1) the area of any peak corresponding to impurity F, when multiplied by a correction factor of 1.8, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

**Related substances**

Prepare fresh solutions and perform the tests without delay.

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

Maintain the column temperature at 60°C.

As the mobile phase, use a solution prepared as follows: mix 12 volumes of tetrahydrofuran R, 23 volumes of acetonitrile R and 65 volumes of water R and filter.

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

For solution (1) dissolve 20 mg of Medroxyprogesterone acetate and dilute to 10.0 mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3) dilute 1.0 mL of solution (2) to 10.0 mL. For solution (4) dissolve 4 mg of medroxyprogesterone acetate for system suitability RS (containing medroxyprogesterone acetate and the impurities A, B, C, D, E, G and I) and dilute to 2.0 mL.

Operate with a flow rate of 0.9 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm.

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

Use the chromatogram supplied with medroxyprogesterone acetate for system suitability RS and the chromatogram obtained with solution (4) to identify the peaks due to impurities A, B, C, D, E, G and I. The impurities are eluted at the following relative retention with reference to the peak of medroxyprogesterone acetate (retention time about 27 minutes): impurity A about 0.3; impurity I about 0.5; impurity H about 0.65; impurity B about 0.7; impurity C about 0.8; impurity G about 0.85; impurity D about 0.9; impurity E about 0.95.

The test is not valid unless in the chromatogram obtained with solution (4) the resolution factor between the peaks due to impurity G and due to medroxyprogesterone acetate is at least 3.3.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity D is not greater than the area of the principal peak obtained with solution (2) (1.0%);
- the area of any peak corresponding to impurity B is not greater than 0.7 times the area of the principal peak obtained with solution (2) (0.7%);
- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 1.5, is not greater than 3 times of the area of the principal peak obtained with solution (3) (0.3%);
- the area of any peak corresponding to impurity G, when multiplied by a correction factor of 2.6, is not greater than 2 times of the area of the principal peak obtained with solution (3) (0.2%);
- the area of any peak corresponding to impurity C, E or I is not greater than 2 times the area of the principal peak obtained with solution (3) (0.2%).
• the area of any other impurity peak is not greater than the area of the principal peak obtained with solution (3) (0.1%);

• the sum of the areas (corrected where necessary) of all the peaks, other than the principal peak, is not greater than 1.5 times the area of the principal peak obtained with solution (2) (1.5%). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (3) (0.05%).

**Assay**

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

Measure the absorbance of the diluted solution in a 1 cm layer at the maximum at about 241 nm and calculate the content of \( \text{C}_{24}\text{H}_{34}\text{O}_{4} \) using the absorptivity value of 42.6 \( (\varepsilon_{1%} = 426) \)

**Impurities**

A. 6β-hydroxy-6α-methyl-3,20-dioxopregn-4-en-17-yl acetate (6-hydroxy(medroxyprogesterone acetate)),

B. 17-hydroxy-6α-methylpregn-4-ene-3,20-dione (medroxyprogesterone),

C. 6α,17αβ-dimethyl-3,17-dioxo-D-homopregn-4-en-17αα-yl acetate,

D. 6β-methyl-3,20-dioxopregn-4-en-17-yl acetate (6-epi-medroxyprogesterone acetate),
E. 6-methylidene-3,20-dioxopregn-4-en-17-yl acetate (6-methylidenehydroxyprogesterone acetate),

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

G. 6-methyl-3,20-dioxopregna-4,6-dien-17-yl acetate (megestrol acetate),

H. 3,20-dioxopregn-4-en-17-yl acetate (hydroxyprogesterone acetate),

I. 17αβ-hydroxy-6α,17αα-dimethyl-D-homopregn-4-ene-3,17-dione.
Medroxyprogesterone injection
(*Medroxyprogesteroni injectio*)

This is a draft proposal of a revised monograph for *The International Pharmacopoeia* (Working document QAS/16.670, June 2016). The working document with line numbers and tracked changes 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.** Contraceptive.

**Storage.** Medroxyprogesterone injection should be protected from light. On standing solid matter may separate; it should be resuspended before use.

**Additional information.** Strength in the current WHO Model List of Essential Medicines: 150 mg/mL in 1 mL vial.

**Requirements**

Complies with the monograph for Parenteral preparations.

**Definition.** Medroxyprogesterone injection is a sterile aqueous suspension of Medroxyprogesterone acetate. It contains not less than 90.0% and not more than 110.0% of the amount of Medroxyprogesterone acetate (C\textsubscript{24}H\textsubscript{34}O\textsubscript{4}) stated on the label.

**Identity tests**

- Either test A alone or tests B and C or tests C and D may be applied.
  
  A. Centrifuge a volume of the injection to be examined containing 50 mg of Medroxyprogesterone acetate. Decant the supernatant liquid and discard. Dry the residue at 105°C for 3 hours and carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from medroxyprogesterone acetate RS or with the reference spectrum of medroxyprogesterone acetate.
  
  B. Carry out test B.1 or, where UV detection is not available, test B.2.
  
  B.1 Carry out the test as described under 1.14.1 Thin-layer chromatography using silica R5 as the coating substance and a mixture of 10 volumes of dichloromethane R and 1 volume of ethyl acetate R as the mobile phase. Apply separately to the plate 10 μL of each of the following three solutions in dichloromethane R. For solution (A) measure a volume of injection to be examined containing about 40 mg of Medroxyprogesterone acetate, add 15 mL of dichloromethane R, shake vigorously for
20 minutes, allow to stand for 30 minutes, add 2.5 g sodium sulphate anhydrous R, shake for 5 minutes and allow to stand for another 10 minutes. For solution (B) use 2.5 mg of medroxyprogesterone acetate RS per mL. After removing the plate from the chromatographic chamber heat it at 120°C for 30 minutes, spray with 4-toluenesulphonic acid/ethanol TS and heat further at 120°C for 10 minutes. Allow the plate to cool and examine the chromatogram in ultraviolet light (365 nm).

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

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography using the conditions described under test B.1, but spray the plate with a mixture of equal volumes of sulfuric acid R and ethanol (~750 g/L) TS and heat further at 120°C for 10 minutes. Allow the plate to cool and examine the chromatogram in daylight.

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

C. Centrifuge a volume of injection to be examined containing 30 mg of Medroxyprogesterone acetate. Decant the supernatant liquid, dissolve the residue in 5 mL of sulfuric acid R and introduce 5 mL of ethanol (~750 g/L) TS to form an upper layer; a bluish violet ring is formed at the interface of the two layers.

D. See the test described below under “Assay”. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).

pH. pH of the injection, 3.0–7.0.

Impurity F (4,5-Dihydmroxyprogesterone acetate). Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R5 as the coating substance and a mixture of 10 volumes of tetrahydrofuran R, 45 volumes of tert-butyl methyl ether R and 45 volumes of hexane R as the mobile phase.

Apply separately to the plate 10 µL of each of the following three solutions in dichloromethane R. For solution (A) accurately measure a volume of injection to be examined containing 300 mg of Medroxyprogesterone acetate, add 15 mL of dichloromethane R, shake vigorously for 20 minutes, allow to stand for 30 minutes, add 10 g sodium sulphate anhydrous R, shake for 5 minutes and allow to stand for another 10 minutes. For solution (B) dilute 0.5 volume of solution (1) to 100 volumes. For solution (C) use 20 mg of medroxyprogesterone acetate RS and 0.1 mg of medroxyprogesterone acetate impurity F RS per mL.

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

In the chromatogram obtained with solution (C) impurity F has a Rf value of about 0.66 and medroxyprogesterone acetate an Rf value of about 0.56. The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots. In the chromatogram obtained with solution (A) any spot due to impurity F is not more intense than the corresponding spot in the chromatogram obtained with solution (B) (0.5%).

Related substances
Prepare fresh solutions and perform the tests without delay.
Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”.

Prepare the following solutions with the mobile phase. For solution (1) dilute a suitable volume of the injection to be examined to obtain a concentration of 0.4 mg of Medroxyprogesterone acetate per mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3) dissolve 4 mg of medroxyprogesterone acetate for system suitability RS (containing medroxyprogesterone acetate and the impurities A, B, C, D, E, G and I) and dilute to 2.0 mL. For solution (4) use 3.65 μg of methyl hydroxybenzoate R and 0.4 μg of propyl hydroxybenzoate R per mL.

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

Use the chromatogram supplied with medroxyprogesterone acetate for system suitability RS and the chromatogram obtained with solution (4) to identify the peaks due to impurities A, B, C, D, E, G and I. The impurities are eluted at the following relative retention with reference to the peak of medroxyprogesterone acetate (retention time about 27 minutes): impurity A about 0.3; impurity I about 0.5; impurity H about 0.65; impurity B about 0.7; impurity C about 0.8; impurity G about 0.85; impurity D about 0.9; impurity E about 0.95.

The test is not valid unless the resolution factor between the peaks due to medroxyprogesterone acetate and due to impurity G is at least 3.3.

In the chromatogram obtained with solution (1):

• the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);

• the sum of the areas of all peaks, other than the principal peak, is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak due to hydroxybenzoate derivatives in the chromatogram obtained with solution (4). Disregard any peak with an area less than 0.05 times the area of the principal peak obtained with solution (2) (0.05%).

Assay

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

As the mobile phase use a solution prepared as follows: mix 100 volumes of tetrahydrofuran R, 350 volumes of acetonitrile R and 500 volumes of water R.

Prepare the following solutions in the mobile phase. For solution (1) dilute a suitable volume of the injection to be examined to obtain a concentration of 40 μg of Medroxyprogesterone acetate per mL. For solution (2) dissolve 10 mg of medroxyprogesterone acetate RS in 50 mL. Dilute 5 mL of this solution to 25 mL.

Operate with a flow rate of 0.9 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 241 nm.

Inject separately 20 μL of solution (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of medroxyprogesterone acetate \( \left( \text{C}_{24}\text{H}_{34}\text{O}_{4} \right) \), using the declared content of \( \text{C}_{24}\text{H}_{34}\text{O}_{4} \) in medroxyprogesterone acetate RS.

***
Clindamycin palmitate hydrochloride

(\textit{Clindamycini palmitas hydrochloridum})

This is a draft proposal of a monograph for \textit{The International Pharmacopoeia} (Working document QAS/16.654, July 2016).

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: schmidt@who.int.

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

Relative molecular mass. 699.85

Graphic formula

\begin{center}
\includegraphics[width=0.5\textwidth]{molecular_formula.png}
\end{center}

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

Description. A white or almost white powder.

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

Category. Antibacterial.

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

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

Requirements

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

Identity tests

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

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from clindamycin palmitate hydrochloride RS or with the reference spectrum of clindamycin palmitate hydrochloride.
B. Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Assay”. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

C. Dissolve about 10 mg in 2 mL of hydrochloric acid (~200 g/L) TS and heat on a water-bath for 3 minutes. Add 3 mL of sodium carbonate (106 g/L) TS and 1 mL of sodium nitroprusside (20 g/L) TS. A violet-red colour develops [test to be verified].

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

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

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

**Sulfated ash.** Not more than 5 mg/g.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a column (25 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 μm). 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>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–30</td>
<td>100 to 0</td>
<td>0 to 100</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>30–80</td>
<td>0</td>
<td>100</td>
<td>Isocratic</td>
</tr>
<tr>
<td>80–81</td>
<td>0 to 100</td>
<td>100 to 0</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>81–90</td>
<td>100</td>
<td>0</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Prepare the following solutions in methanol R. For solution (1) dissolve 100 mg of clindamycin palmitate hydrochloride and dilute to 10.0 mL. For solution (2) dilute 2.0 mL of solution (1) to 100 mL. For solution (3) dissolve about 74 mg clindamycin palmitate hydrochloride RS (containing clindamycin palmitate hydrochloride and impurity A) and dilute to 10.0 mL.

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

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

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

In the chromatogram obtained with solution (1):

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

1 Agilent Zorbax Elipse XDB- C8 has been found suitable.
Assay

[The method is currently under validation. Some parameters need to be amended.]

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

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

Prepare the following solutions in mobile phase. For solution (1) transfer 50.0 mg of clindamycin palmitate hydrochloride into a 50 mL volumetric flask and dilute to volume. For solution (2) dissolve 50 mg of clindamycin palmitate hydrochloride RS (containing clindamycin palmitate hydrochloride and impurity A) into a 50 mL volumetric flask and dilute to 50.0 mL.

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

Inject alternately 20 μL each of solutions (1) and (2). The retention time of clindamycin palmitate is about x minutes. The assay is not valid unless in the chromatogram obtained with solution (2) the resolution between the peaks due to clindamycin palmitate and to impurity A (relative retention time is about x) is at least x.

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

Impurities

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

Reagents to be established

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

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

² Agilent Zorbax Elipse XDB- C8 has been found suitable.
Clindamycin palmitate for oral suspension
(Clindamycini palmitas ad suspensionem peroralem)

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

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. Antibacterial.

Storage. Clindamycin palmitate hydrochloride for oral suspension should be kept in a tightly closed container.

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

Labelling. The designation on the container of clindamycin palmitate for oral suspension should state that the active ingredient is clindamycin palmitate hydrochloride and the quantity should be indicated in terms of equivalent amount of clindamycin.

Requirements

Complies with the monograph for Liquid preparations for oral use; the powder complies with the section of the monograph entitled “Powders for oral solutions, oral suspensions and oral drops”.

Definition. Clindamycin palmitate for oral suspension is a suspension of Clindamycin palmitate hydrochloride in a suitable vehicle, which may be flavoured. It is prepared from the powder as stated on the label just before issue for use. When freshly constituted the oral suspension contains not less than 90.0% and not more than 110.0% of the labelled amount of clindamycin (C₁₈H₃₃ClN₂O₅S).

Identity tests

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

pH value. pH of a solution constituted as directed in the labelling, 2.5–5.0.

Loss on drying. Dry the powder for oral suspension to constant mass at 60°C under reduced pressure; it loses not more than 20 mg/g.

Related substances

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

Use the following conditions for gradient elution:

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

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

Prepare the following solutions in methanol R. For solution (1) transfer a quantity of the oral suspension, equivalent of about 57 mg of clindamycin to a 10 mL volumetric flask and dilute to volume. For solution (2) dilute 2.0 ml of solution (1) to 100.0 mL. For solution (3) dissolve about 74 mg clindamycin palmitate hydrochloride RS (containing clindamycin palmitate hydrochloride and impurity A) and dilute to 10.0 mL.

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

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

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

In the chromatogram obtained with solution (1):

• the area of any impurity peak is not more than the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

**Assay**

*The method is currently under validation. Some parameters need to be amended.*

Use the oral suspension immediately after preparation.

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

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

Prepare the following solutions in the mobile phase. For solution (1) dissolve a quantity of the oral suspension, equivalent to about 225 mg of clindamycin, accurately weighed, and dilute to 50.0 mL, filter and use the filtrate. For solution (2) dissolve about 74 mg clindamycin palmitate hydrochloride RS (containing clindamycin palmitate hydrochloride and impurity A) and dilute to 10.0 mL.

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

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1 Agilent Zorbax Elipse XDB- C8 (4.6 × 250 mm, 5 μm) has been found suitable.
2 Agilent Zorbax Elipse XDB- C8 has been found suitable.
Inject alternately 20 μL each of solutions (1) and (2). The retention time of clindamycin palmitate is about x minutes. The assay is not valid unless in the chromatogram obtained with solution (2) the resolution between the peaks due to clindamycin palmitate and impurity A (relative retention time is about x) is at least x.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2). Determine the weight per mL (1.3.1) of the oral suspension and calculate the percentage content of clindamycin (C_{18}H_{33}ClN_{2}O_{5}S) in the oral suspension, using the declared content of clindamycin palmitate hydrochloride (C_{34}H_{63}ClN_{2}O_{6}S.HCl) in clindamycin palmitate hydrochloride RS. Each mg of clindamycin palmitate hydrochloride (C_{34}H_{63}ClN_{2}O_{6}S.HCl) is equivalent to 0.607 mg clindamycin (C_{18}H_{33}ClN_{2}O_{5}S).

**Impurities**

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

***
Clindamycin phosphate
(Clindamycini phosphas)

This is a draft proposal of a revised monograph for The International Pharmacopoeia (Working document QAS/16.678, August 2016).

The working document with line numbers and tracked changes 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.

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

\[
\text{C}_{18}\text{H}_{34}\text{ClN}_{2}\text{O}_{8}\text{PS}
\]

**Relative molecular mass.** 505.0

**Chemical name**

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

**Solubility.** Freely soluble in water; very slightly soluble in ethanol (~750 g/L) TS and acetone R, practically insoluble in dichloromethane R.

**Category.** Antibacterial.

**Storage.** Clindamycin phosphate should be kept in a tightly closed container.

**Additional information.** Clindamycin phosphate is slightly hygroscopic and may exhibit polymorphism. It is a semi-synthetic product derived from a fermentation product.

**Requirements**
Clindamycin phosphate contains not less than 96.0% and not more than 102.0% of \(\text{C}_{18}\text{H}_{34}\text{ClN}_{2}\text{O}_{8}\text{PS}\), calculated with reference to the anhydrous substance.

- Either tests A and D or tests B, C and D may be applied.
A. Carry out the examination as described under **1.7 Spectrophotometry in the infrared region.** The infrared absorption spectrum is concordant with the spectrum obtained from clindamycin phosphate RS or with the *reference spectrum* of clindamycin phosphate. If the spectra thus obtained are not concordant repeat the test using the residues obtained. Separately dissolve the test substance and clindamycin phosphate RS in a small amount of water R and heat until the substances are completely dissolved. Evaporate to dryness under reduced pressure and dry the residues at 100–105°C for 2 hours. The infrared absorption spectrum is concordant with the spectrum obtained from clindamycin phosphate RS.

B. Carry out the test as described under **1.14.1 Thin-layer chromatography** using silica gel R3 as the coating substance and a mixture of 6 volumes of 1-butanol R, 2 volumes of water and 2 volumes of glacial acetic acid R as the mobile phase. Apply separately to the plate 5 μL of each of 3 solutions in methanol R containing (A) 2.0 mg of Clindamycin phosphate per mL, (B) 2.0 mg of clindamycin phosphate RS and for solution (C) dissolve 10 mg of lincomycin hydrochloride RS in 5 mL of solution B. After removing the plate from the chromatographic chamber allow it to dry at 105°C for 30 minutes and spray with potassium permanganate (1 g/L) TS. Examine the chromatogram in daylight. The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B. The test is not valid unless the chromatogram obtained with solution C shows two clearly separated spots.

C. Dissolve 10 mg in 2 mL of hydrochloric acid (~70 g/L) TS and heat directly in a flame for 1 minute; a disagreeable sulfurous odour is perceptible. Cool, add 4 mL of sodium carbonate (75 g/L) TS and 0.5 mL of sodium nitroprusside (45 g/L) TS; a violet-red ring is formed that fades quickly.

D. Boil 0.1 g under a reflux condenser with a mixture of 5 mL of sodium hydroxide (~400 g/L) TS and 5 mL of water for 90 minutes. Cool and add 5 mL of nitric acid (~1000 g/L) TS. Extract with three 15 mL quantities of dichloromethane R and discard the extracts. Filter the aqueous layer through a paper filter; the filtrate yields reaction B described under **2.1 General identification tests** as characteristic of orthophosphates.

**Specific optical rotation.** Use a 10 mg/mL solution and calculate with reference to the anhydrous substance; [α]<sub>D</sub><sup>20°C</sup> = +115° to +130°.

**Clarity and colour of solution.** Dissolve 1.00 g in carbon dioxide-free water R. Heat gently if necessary. Cool and dilute to 25.0 mL with carbon dioxide-free water R. This solution is clear and colourless, when analysed as described under **1.11.2 Degree of coloration of liquids, Method II.**

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

**Water.** Determine as described under **2.8 Determination of water by the Karl Fischer method, method A,** using 0.2 g of the substance; the water content is not more than 0.050 g/g.

**pH value.** pH of a 10 mg/mL solution in carbon-dioxide-free water R, 3.5–4.5.

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

<sup>1</sup> A Symmetry C18 column was found suitable.
Use the following conditions for gradient elution:

- Mobile phase A: 21 volumes of acetonitrile for chromatography R and 79 volumes of phosphate buffer pH 6.0;
- Mobile phase B: 60 volumes of acetonitrile for chromatography R and 40 volumes of phosphate buffer pH 6.0.

Prepare the phosphate buffer pH 6.0 by dissolving 13.6 g of potassium dihydrogen phosphate R in 750 mL of water R, adjust the pH to 6.0 with potassium hydroxide (~450 g/L) TS and dilute to 1000 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>0–13</td>
<td>100</td>
<td>0</td>
<td>Isocratic</td>
</tr>
<tr>
<td>13–18</td>
<td>100 to 50</td>
<td>0 to 50</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>18–39</td>
<td>50</td>
<td>50</td>
<td>Isocratic</td>
</tr>
<tr>
<td>39–40</td>
<td>50 to 100</td>
<td>50 to 0</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>40–55</td>
<td>100</td>
<td>0</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate with a flow rate of 1.1 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 210 nm. Maintain the column temperature at 30°C.

Prepare the following solutions in mobile phase A.

For solution (1) dissolve about 30 mg of the test substance and dilute to 10 mL. For solution (2) dilute 1.0 mL of solution (1) to 200.0 mL. For solution (3) dilute 2.0 mL of solution (2) to 10.0 mL. For solution (4) dissolve 3.0 mg of clindamycin phosphate for system suitability RS (containing clindamycin phosphate and the impurities B, E, F, G, I, J, K and L) and dilute to 1.0 mL.

Inject 20 μL of solution (4).

Use the chromatogram obtained with solution (4) and the chromatogram supplied with clindamycin phosphate for system suitability RS to identify the peaks due to the impurities B, E, F, G, I, J, K and L. The impurities are eluted at the following relative retention with reference to clindamycin phosphate (retention time about 12 minutes): impurity F about 0.15; impurity G about 0.19; impurity I about 0.34; impurity B about 0.45; impurity L about 0.64; impurity J about 1.20; impurity E about 1.73; and impurity K about 1.90.

The test is not valid unless the resolution between the peaks due to impurity F and the peak due to impurity G is at least 2.0.

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

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to either impurity B or L is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);
- the area of any peak corresponding to either impurity E or F is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);
- the area of any peak corresponding to either impurity G, I, J or K is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);
- the area of any other impurity peak is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.10 %);
- the sum of the areas of all impurities is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (2.0 %). Disregard any peak with an area less
than 0.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.05%).

**Assay**

Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).²

As the mobile phase use a mixture of 21 volumes of acetonitrile for chromatography R and 79 volumes of phosphate buffer pH 6.0. Prepare the phosphate buffer pH 6.0 by dissolving 13.6 g of potassium dihydrogen phosphate R in 750 mL of water R, adjust the pH to 6.0 with potassium hydroxide (~450g/L) TS and dilute to 1000 mL with water R.

Prepare the following solutions in mobile phase. For solution (1) dissolve about 30 mg of the test substance and dilute to 10 mL. For solution (2) dissolve 30 mg of Clindamycin phosphate and dilute to 10.0 mL. For solution (3) use a solution containing 0.12mg lincomycin per mL and 0.24 mg of clindamycin phosphate RS per mL.

Operate with a flow rate of 1.1 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 210 nm.

Inject 20 µL of solution (3). In the chromatogram the following peaks are eluted at the following relative retentions with reference to clindamycin phosphate (retention time about 8.0 minutes): lincomycin about 0.32. The assay is not valid unless the resolution between the peaks due to clindamycin phosphate and lincomycin is at least 7.0.

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

Measure the areas of the peaks corresponding to clindamycin phosphate obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of clindamycin phosphate \((C_{18}H_{34}ClN_2O_8PS)\), using the declared content of clindamycin phosphate \((C_{18}H_{34}ClN_2O_8PS)\) in clindamycin phosphate RS.

**Additional requirements for Clindamycin phosphate for parenteral use**

Complies with the monograph for Parenteral preparations.

**Bacterial endotoxins.** If intended for use in the manufacture of a parenteral dosage form without a further appropriate procedure for the removal of bacterial endotoxins, carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 0.6 IU of endotoxin RS per mg of clindamycin.

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

**Impurities**

A. Methyl 6,8-dideoxy-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-D-erythro-α-D-galacto-octopyranoside (lincomycin) (degradation product)

² A Symmetry C18 column was found suitable.
B. Methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-4-ethyl-1-methylpyrrolidin-2-yl]carbonyl]amino]-2-O-phosphono-1-thio-L-threo-α-D-galacto-octopyranoside (clindamycin B-2-phosphate) (synthesis-related impurity)

C. Methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-3-O-phosphono-1-thio-L-threo-α-D-galacto-octopyranoside (clindamycin-3-phosphate) (synthesis-related impurity)

D. Methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-4-O-phosphono-1-thio-L-threo-α-D-galacto-octopyranoside (clindamycin-4-phosphate) (synthesis-related impurity)

E. Methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-L-threo-α-D-galacto-octopyranoside (clindamycin) (synthesis-related impurity / degradation product)
F. Methyl 6,8-dideoxy-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-2-O-phosphono-1-thio-D-erythro-α-D-galacto-octopyranoside (lincomycin 2-phosphate) (degradation product)

G. Methyl 6,8-dideoxy-2,4-O-(hydroxyphosphoryl)-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-D-erythro-α-D-galacto-octopyranoside (2,4-phosphatidyl lincomycin) (synthesis-related impurity)

H. Methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-2,3-di-O-phosphono-1-thio-L-threo-α-D-galacto-octopyranoside (clindamycin-2,3-bisphosphate) (synthesis-related impurity)

I. Methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-2,4-di-O-phosphono-1-thio-L-threo-α-D-galacto-octopyranoside (clindamycin 2,4-bisphosphate)
J. Methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S)-1-methyl-4-propyldenepyrrolidin-2-yl]carbonyl]amino]-2-O-phosphono-1-thio-L-threo-α-D-galacto-octopyranoside (propylidene analog of clindamycin 2-phosphate)

K. 2,2′-Oxybis(hydroxyphosphoryl)bis[methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-L-threo-α-D-galacto-octopyranoside] (diclindamycin pyrophosphate)

L. Methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-2-O-phosphono-1-thio-D-erythro-α-D-galacto-octopyranoside (7-epiclindamycin 2-phosphate) (degradation product)

**Reagents to be established**

**Potassium hydroxide (~450g/L) TS**

A solution of potassium hydroxide R containing about 450 g of KOH per litre.

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

**Category.** Antibacterial.

**Storage.** Clindamycin injection should be stored at a temperature not exceeding 30°C. It should not be refrigerated and it should not be allowed to freeze.

**Additional information.** Strength in the current WHO Model List of Essential Medicines (EML): 150 mg (as phosphate) per mL. Strengths in the current EML for Children: 150 mg (as phosphate) per mL.

**Labelling.** The designation of the container should state that the active ingredient is the phosphate form and the quantity should be indicated in terms of equivalent amount of clindamycin.

**Requirements**

Complies with the monograph for Parenteral preparations.

**Definition.** Clindamycin phosphate injection is a sterile solution of Clindamycin phosphate in water for injections. It contains not less than 90.0% and not more than 110.0% of the amount of clindamycin $C_{18}H_{33}ClN_2O_5S$ stated on the label.

**Identity tests**

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

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

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R3 as the coating substance and a mixture of 20 volumes of glacial acetic acid R, 20 volumes of water R and 60 volumes of 1-butanol R as the mobile phase. Apply separately to the plate 5 μL of each of the following 3 solutions in methanol R. For solution (A) dilute a quantity of the injection to obtain a solution containing the equivalent of 2.0 mg of Clindamycin per mL. For solution (B) use clindamycin phosphate RS to obtain a solution containing 2.0 mg of clindamycin phosphate per mL. For solution (C) dissolve 10 mg of lincomycin hydrochloride RS in 5 mL of solution (B). After removing the plate from the chromatographic chamber, allow it to dry at 105°C for 30 minutes. Spray the plate with potassium permanganate (1 g/L) TS and examine the chromatogram in daylight.
The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B). The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

C. Boil 1 mL of the injection under a reflux condenser with a mixture of 5 mL of sodium hydroxide (~400 g/L) TS and 5 mL of water for 90 minutes. Cool and add 5 mL of nitric acid (~1000 g/L) TS. Extract with three 15 mL quantities of dichloromethane R and discard the extracts. Filter the upper aqueous layer through a paper filter; the filtrate yields reaction B described under 2.1 General identification tests as characteristic of orthophosphates.

**pH value (1.13).** pH of the injection, 5.5–7.0.

**Related substances**

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

Use the following conditions for gradient elution:

- mobile phase A: 21 volumes of acetonitrile for chromatography R and 79 volumes of phosphate buffer pH 6.0;
- mobile phase B: 60 volumes of acetonitrile for chromatography R and 40 volumes of phosphate buffer pH 6.0.

Prepare the phosphate buffer pH 6.0 by dissolving 13.6 g of potassium dihydrogen phosphate R in 750 mL of water R, adjust the pH to 6.0 with potassium hydroxide (~450g/L) TS and dilute to 1000 mL with water R.

<table>
<thead>
<tr>
<th>Time (min)</th>
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<tr>
<td>39–40</td>
<td>50 to 100</td>
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<td>Return to initial composition</td>
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<tr>
<td>40–55</td>
<td>100</td>
<td>0</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate with a flow rate of 1.1 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 210 nm. Maintain the column temperature at 30°C.

Prepare the following solutions in mobile phase A.

For solution (1) dilute 2.0 mL of the injection to 100.0 mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3) use a solution containing 0.12 mg lincomycin hydrochloride RS per mL, 0.24 mg of clindamycin phosphate RS per mL and 15 µg of benzyl alcohol R per mL.

Inject 20 µL of solution (3). The test is not valid unless in the chromatogram obtained with solution (3), the resolution factor between the peaks due to lincomycin and clindamycin phosphate is at least 7.7. The following peaks are eluted at the following relative retentions with reference to clindamycin phosphate (retention time about 12 minutes): lincomycin: about x; benzyl alcohol: about 0.x. [to be added]

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

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1 A Symmetry C18 column was found suitable.
In the chromatogram obtained with solution (1):

• the area of any impurity peak is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (3) (3.0%);

• the sum of the areas of all impurities is not greater than 8 times the area of the principal peak in the chromatogram obtained with solution (2) (8.0%). Disregard any peak due to benzyl alcohol, if present, and any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Assay
Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm × 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).2

As the mobile phase use a mixture of 21 volumes of acetonitrile for chromatography R and 79 volumes of phosphate buffer pH 6.0. Prepare the phosphate buffer pH 6.0 by dissolving 13.6 g of potassium dihydrogen phosphate R in 750 mL of water R, adjust the pH to 6.0 with potassium hydroxide (~450 g/L) TS and dilute to 1000 mL with water R.

Prepare the following solutions in mobile phase. For solution (1) dilute 1.0 mL of the injection to 100.0 mL. For solution (2) dissolve 36 mg of clindamycin phosphate RS and dilute to 20.0 mL. For solution (3) use a solution containing 0.12 mg lincomycin per mL, 0.24 mg of clindamycin phosphate RS per mL and 15 µg of benzyl alcohol R per mL.

Operate with a flow rate of 1.1 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 210 nm.

Inject 20 µL of solution (3). In the chromatogram the following peaks are eluted at the following relative retentions with reference to clindamycin phosphate (retention time about 8.0 minutes): benzyl alcohol about 0.6. The assay is not valid unless the resolution between the peaks due to clindamycin phosphate and benzyl alcohol is at least 3.0 and the resolution between the peaks due to clindamycin phosphate and lincomycin is at least 7.0.

Inject alternately 20 µL each of solutions (1) and (2). Measure the areas of the peaks corresponding to clindamycin phosphate obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of clindamycin (C₁₈H₃₄ClN₂O₈PS) in the injection using the declared content of C₁₈H₃₄ClN₂O₈PS in clindamycin phosphate RS. Each mg of clindamycin phosphate (C₁₈H₃₄ClN₂O₈PS) is equivalent to 0.8416 mg of clindamycin (C₁₈H₃₃ClN₂O₅S).

**Bacterial endotoxins.** Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 0.10 IU of endotoxin RS per mg of clindamycin.

Impurities
The impurities limited by the requirements of this monograph include those listed in the monograph on Clindamycin phosphate.

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2 A Symmetry C18 column was found suitable.
Ceftriaxone sodium
(Ceftriaxonum natricum)

This is a revised draft proposal of a monograph for The International Pharmacopoeia (Working document QAS/15.644/Rev.1, July 2016).

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: schmidt@who.int.

C_{18}H_{16}N_{8}Na_{2}O_{7}S_{3}.3\frac{1}{2}H_{2}O

Relative molecular mass. 661.60


Description. Almost white or yellowish, slightly hygroscopic, crystalline powder.

Solubility. Freely soluble in water, sparingly soluble in methanol, very slightly soluble in anhydrous ethanol.

Labelling. The label states, where applicable:

• that the substance is free of bacterial endotoxins;
• that the substance is sterile.

Category. Antibacterial

Storage. Ceftriaxone sodium should be kept in an air-tight container protected from light. If the substance is sterile, store in a sterile and air-tight container protected from light.

Manufacture. Where necessary, the production method is validated to demonstrate that the substance, if tested, would comply with limits of not more than 20 ppm for N,N-dimethylaniline and 0.8% for 2-ethylhexanoic acid.

Additional information. Ceftriaxone sodium is a semi-synthetic product derived from a fermentation product.

Requirements. Ceftriaxone sodium contains not less than 96.0% and not more than 102.0% of C_{18}H_{16}N_{8}Na_{2}O_{7}S_{3}, calculated with reference to the anhydrous substance.
Identity tests

- Either tests A and C 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 ceftriaxone sodium RS or with the reference spectrum of ceftriaxone sodium.

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

C. When tested for sodium as described under 2.1 General identification tests, yields the characteristic reaction.

Specific optical rotation (1.4). Dissolve 0.250 g in water R and dilute to 25.0 mL with the same solvent. Calculate with reference to the anhydrous substance; $\delta_{d}^{20^\circ} = -155^\circ$ to $-170^\circ$.

Clarity and colour of solution. Dissolve 2.40 g in carbon-dioxide-free water R and dilute to 20.0 mL with the same solvent (Solution A). Dilute 2 mL of Solution A to 20 mL carbon-dioxide-free water R. The solution is clear and not more intensely coloured than reference solution Y₅ or BY₅ when compared as described under 1.11.2 Degree of coloration of liquids. (Keep the remaining solution (Solution A) for the “pH value”.)

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

pH value (1.13). pH of the solution prepared for the “Clarity and colour of solution” (Solution A), 6.0 to 8.0.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, method A, using 0.100 g of the test substance. The water content is not less than 80 mg per g and not more than 110 mg per g.

Bacterial endotoxins. If intended for use in the manufacture of a parenteral dosage form without a further appropriate procedure for the removal of bacterial endotoxins, carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 0.20 IU of endotoxin per mg of ceftriaxone sodium.

Related substances

Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under assay method.

Prepare the following solutions in mobile phase: for solution (1) dissolve about 30 mg of the test substance and dilute to 100.0 mL. For solution (2) dilute 1 volume of solution (1) to 100 volumes. For solution (3) dissolve about 5 mg ceftriaxone sodium RS and 5 mg of ceftriaxone impurity A to 100.0 mL.

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the peaks due to ceftriaxone and ceftriaxone impurity A is at least 3.0. Ceftriaxone impurity A is eluted at a relative retention of about 1.4 with reference to ceftriaxone (retention time about 9 min).

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

- the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);
- the sum of the areas of all peaks, other than the principal peak, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Assay

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

As the mobile phase use a solution prepared as follows: dissolve 2.0 g of tetradeceylammonium bromide R and 2.0 g of tetraheptylammonium bromide R in a mixture of 440 mL of water R, 55 mL of phosphate buffer pH 7.0 (0.067 mol/L) TS, 5.0 mL of citrate buffer pH 5.0 TS and 500 mL of acetonitrile R and filter.

Prepare the following solutions in mobile phase. For solution (1) dissolve 30 mg of the test substance, accurately weighed and dilute to 100.0 mL. For solution (2) dissolve about 30 mg of ceftriaxone sodium RS, accurately weighed and dilute to 100.0 mL. For solution (3) dissolve about 5 mg ceftriaxone sodium RS and about 5 mg of ceftriaxone impurity A and dilute to 100.0 mL.

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

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the peaks due to ceftriaxone and ceftriaxone impurity A is at least 3.0.

Inject alternately 20 µL each of solution (1) and (2). Measure the areas of the peaks corresponding to ceftriaxone and calculate the percentage content of C\(_{18}\)H\(_{16}\)N\(_8\)Na\(_2\)O\(_7\)S\(_3\), using the declared content of C\(_{18}\)H\(_{16}\)N\(_8\)Na\(_2\)O\(_7\)S\(_3\) in ceftriaxone sodium RS.

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

Impurities

[Note from the Secretariat. The structures of the impurities will be added at a later stage.]

A. (6\(R\),7\(R\))-7-[(E)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[(6-hydroxy-2- methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio][methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid (Ceftriaxone E-isomer)

B. (Z)-2-(2-Aminothiazol-4-yl)-N-((5aR,6R)-1,7-dioxo-1,3,4,5a,6,7-hexahydroazeto[2,1-b] furo[3,4-d][1,3]thiazin-6-yl)-2-(methoxyimino)acetamide. (Deacetylcefotaxime lactone)

C. (6\(R\),7\(R\))-7-Amino-3-[(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio][methyl]- 8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (Deacyl ceftriaxone)

D. (Z)-S-Benzothiazol-2-yl 2-(2-aminothiazol-4-yl)-2-(methoxyimino)thioacetate (Ceftriaxone benzothiazolyl oxime)

\(^1\) Hypersil BDS C18 has been found suitable.

F. 3-Mercapto-2-methyl-1,2-dihydro-1,2,4-triazine-5,6-dione. (Ceftriaxone triazine analog)

G. (6R,7R)-7-[(Z)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-1,2,4-triazin-3-yl)thio]methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-3-ene-2-carboxylic acid (Ceftriaxone 3-ene isomer).

**Reagents to be included**

**Citrate buffer, pH 5 TS**

*Procedure.* Dissolve 20.17 g of citric acid R in 800 ml of water R, adjust to pH 5.0 with sodium hydroxide (~400 g/L) TS and dilute to 1000 mL with water R.

**Tetradecylammonium bromide R**

C_{40}H_{84}BrN. Chromatographic reagent grade of commerce.

*Description.* White to almost white crystals, or a crystalline powder.

*Melting point.* 88-89°C.

**Tetraheptylammonium bromide R**

C_{28}H_{60}BrN. Chromatographic reagent grade of commerce.

*Description.* White, flaky powder.

*Melting range.* Between 89-91°C.

***
Ceftriaxone for injection
(Ceftriaxoni ad injectionem)

This is a revised draft proposal of a monograph for The International Pharmacopoeia (Working document QAS/15.645/Rev.1, July 2016).

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: schmidt@who.int.

Description. A white to almost white powder.

Category. Antibacterial.

Storage. Ceftriaxone for injection should be stored in a tightly closed container. The reconstituted solution should be used immediately after preparation.

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

Additional information. Strengths in the current WHO Model List of Essential Medicines (EML): 250 mg, 1 g (as sodium salt) in vial. Strength in the current WHO EML for children: 250 mg, 1 g (as sodium salt) in vial.

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

Requirements

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

Definition. Ceftriaxone for injection is a sterile powder containing Ceftriaxone sodium with or without excipients.

Ceftriaxone for Injection contains not less than 90.0% and not more than 110.0% of the labelled amount of ceftriaxone (C_{18}H_{18}N_{8}O_{7}S_{3}).

Identity tests

- Either tests A and C 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 ceftriaxone sodium RS or with the reference spectrum of ceftriaxone sodium.

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

C. When tested for sodium as described under 2.1 General identification tests, yields the characteristic reaction.
**Water.** Determine as described under 2.8 Determination of water by the Karl Fischer method, method A, using about 0.100 g of the powder. The water content is not more than 110 mg per g.

**Clarity and colour of solution.** Dissolve 2.40 g in carbon-dioxide-free water R and dilute to 20.0 mL with the same solvent (Solution A). Dilute 2 mL of Solution A to 20 mL carbon-dioxide-free water R. The solution is clear and not more intensely coloured than reference solution YW2 when compared as described under 1.11 Colour of liquids. (Keep the remaining solution (Solution A) for the “pH value”.)

**pH value (1.13).** pH of the solution prepared for the “Clarity and colour of solution” (Solution A), 6.0 to 8.0.

**Bacterial endotoxins.** Carry out the test described under 3.4 Test for bacterial endotoxins, contains not more than 0.20 IU of endotoxin per mg of ceftriaxone.

**Related substances**

Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given below under assay method.

Prepare the following solutions in mobile phase: for solution (1) dissolve about 30 mg of the powder and dilute to 100.0 mL. For solution (2) dilute 1 volume of solution (1) to 100 volumes. For solution (3) dissolve about 5 mg ceftriaxone sodium RS and 5 mg of ceftriaxone impurity A to 100.0 mL.

Inject 20 μL of solution (3). The test is not valid unless the resolution factor between the peaks due to ceftriaxone and ceftriaxone impurity A is at least 3.0. Ceftriaxone impurity A is eluted at a relative retention of about 1.4 with reference to ceftriaxone (retention time about 9 min).

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

In the chromatogram obtained with solution (1):

- the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0 %);
- the sum of the areas of all peaks, other than the principal peak, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (2.5%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

**Assay**

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

As the mobile phase use a solution prepared as follows: dissolve 2.0 g of tetracetyltrimmonium bromide R and 2.0 g of tetraheptyltrimmonium bromide R in a mixture of 440 mL of water R, 55 mL of phosphate buffer, pH 7.0 (0.067 mol/L) TS, 5.0 mL of a citrate buffer pH 5.0 TS and 500 mL of acetonitrile R and filter.

Prepare the following solutions in mobile phase: for solution (1) determine the weight of the contents of 10 containers. Transfer a quantity of the mixed contents containing about 30 mg of ceftriaxone, accurately weighed, to a 100 mL volumetric flask, dissolve and dilute to volume.

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\(^1\) Hypersil BDS C18 has been found suitable.
For solution (2) dissolve about 35 mg of ceftriaxone sodium RS, accurately weighed and dilute to 100.0 mL. For solution (3) dissolve about 5 mg ceftriaxone sodium RS and 5 mg of ceftriaxone impurity A to 100.0 mL.

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

Inject 20 µL of solution (3). The test is not valid unless the resolution factor between the peaks due to ceftriaxone and ceftriaxone impurity A is at least 3.0.

Inject 20 µL of solution (1) and (2). Measure the areas of the peaks corresponding to ceftriaxone and calculate the content of ceftriaxone (C_{18}H_{16}N_8O_7S_3) per container, using the declared content of C_{18}H_{16}N_8Na_2O_7S_3 in ceftriaxone sodium RS. Each mg of C_{18}H_{16}N_8Na_2O_7S_3 is equivalent to 0.9274 mg of C_{18}H_{16}N_8O_7S_3.

**Impurities**

The impurities limited by the requirements of this monograph include those listed in the monograph for Ceftriaxone sodium.
Mebendazole
(Mebendazolum)

This is a draft proposal of a revised monograph for *The International Pharmacopoeia* (Working document QAS/16.674, July 2016).

The working document with line numbers and tracked changes 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.

[Note from the Secretariat. It is proposed to revise the monograph on Mebendazole of The International Pharmacopoeia.]

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

\[
\begin{align*}
\text{C}_{16}\text{H}_{13}\text{N}_{3}\text{O}_{3} \\
\text{Relative molecular mass.} & \quad 295.3 \\
\text{Chemical name.} & \quad \text{Methyl 5-benzoyl-2-benzimidazolocarbamate; methyl (5-benzoyl-1H-benzimidazol-2-yl)carbamate; CAS Reg. No. 31431-39-7.} \\
\text{Description.} & \quad \text{A white or almost white powder.} \\
\text{Solubility.} & \quad \text{Practically insoluble in water, dilute mineral acids and ethanol (~750 g/L) TS ; freely soluble in formic acid (~1080 g/L) TS.} \\
\text{Category.} & \quad \text{Anthelmintic.} \\
\text{Storage.} & \quad \text{Mebendazole should be kept in a well-closed container, protected from light.} \\
\text{Additional information.} & \quad \text{Mebendazole exhibits polymorphism.}
\end{align*}
\]

**Requirements**

**Definition.** Mebendazole is polymorph C, the crystal form of mebendazole RS. Mebendazole contains not less than 99.0% and not more than 101.0% of mebendazole (C_{16}H_{13}N_{3}O_{3}), calculated with reference to the dried substance.
Identity test
Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum obtained from the solid state is concordant with the spectrum obtained from mebendazole RS (confirmation of polymorphic form C).

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to Method A; not more than 20 μg/g.

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

Loss on drying. Dry at 105°C under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) for 4 hours; it loses not more than 5.0 mg/g.

Related substances
Carry out the test as described under 1.14.4 High-performance liquid chromatography using 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 (minutes)</th>
<th>Mobile phase A (%v/v)</th>
<th>Mobile phase B (%v/v)</th>
<th>Comments</th>
</tr>
</thead>
<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>
</tr>
<tr>
<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.

Prepare the following solutions in dimethylformamide R. For solution (1) dissolve 25.0 mg of the test substance and dilute to 25.0 mL. For solution (2) dissolve 1.0 mL of solution (1) to 100.0 mL. Dilute 5.0 mL of this solution to 20.0 mL. For solution (3) dissolve 5.0 mg of mebendazole for system suitability RS (containing the impurities A, B, C, D, E, F and G) and dilute to 5.0 mL.

Inject 10 μL of solution (3). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 4, where Hp is the height above the baseline of the peak due to impurity D (relative retention about 1.1) and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mebendazole (retention time about 12 minutes).

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

Use the chromatogram obtained with solution (3) and the chromatogram supplied with mebendazole for system suitability RS to identify the peaks due to the impurities A, B, C, D, E, F and G. The impurities are eluted at the following relative retention with reference to mebendazole (retention time about 12 minutes): impurity A about 0.4; impurity B about 0.5; impurity C about 1.1; impurity D about 2.5; impurity E about 3.0; impurity F about 8.0; impurity G about 20.0.

¹ A HYPERSIL BDS C₁₈ column has been found suitable.
impurity C about 0.7; impurity D about 1.1; impurity E about 1.3; impurity F about 1.4 and
impurity G about 1.6.

In the chromatogram obtained with solution (1):

• the area of any peak corresponding to impurity A, impurity B, impurity C, impurity D, impurity
  E or impurity F is not greater than the area of the principal peak in the chromatogram
  obtained with solution (2) (0.25%);
• the area of any peak corresponding to impurity G, when multiplied by a correction factor of
  1.4, is not greater than twice the area of the principal peak in the chromatogram obtained
  with solution (2) (0.5%);
• the area of any other impurity peak is not greater than 0.4 times the area of the principal
  peak in the chromatogram obtained with solution (2) (0.10%);
• the sum of the areas of all impurities is not greater than 4 times the area of the principal peak
  in the chromatogram obtained with solution (2) (1.0%). Disregard any peak with an area less
  than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2)
  (0.05%).

Assay. Dissolve about 0.250 g, accurately weighed, in 3 mL of anhydrous formic acid
R and add 50 mL of a mixture of 1 volume of anhydrous acetic acid R and 7 volumes of
methyl ethyl ketone R. Titrate with perchloric acid (0.1 mol/L) VS, determining the end-point
potentiometrically as described under 2.6 Non-aqueous titration.

Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 29.53 mg of C_{16}H_{13}N_{3}O_{3}.

Impurities

A. (2-Amino-1H-benzimidazol-5-yl)phenylmethanone

B. (2-Hydroxy-1H-benzimidazol-5-yl)phenylmethanone

C. (2-Amino-1-methyl-1H-benzimidazol-5-yl)phenylmethanone
D. Methyl (5-benzoyl-1-methyl-1H-benzimidazol-2-yl)carbamate

E. Ethyl (5-benzoyl-1H-benzimidazol-2-yl)carbamate

F. Methyl [5-(4-methylbenzoyl)-1H-benzimidazol-2-yl]carbamate

G. N,N′-bis(5-benzoyl-1H-benzimidazol-2-yl)urea
Mebendazole chewable tablets  
(Mebendazoli compressi manducabili)

This is a draft proposal of a revised monograph for The International Pharmacopoeia (Working document QAS/16.661, July 2016).

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: schmidt@who.int.

(Note from the Secretariat. The draft revision of the monograph is based on samples received in response to a letter sent out to pharmaceutical manufacturers in November 2014, inviting their collaborating in the development of this document. Manufacturers that have not yet donated samples and/or specifications are again kindly invited to do so. For more information, kindly contact Dr Herbert Schmidt at schmidt@who.int.)

Category. Anthelmintic.

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

Labelling. The designation on the container should state that the tablets may be chewed, swallowed whole, crushed and mixed with food or liquid or dispersed in water.

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 chewable tablets contain Mebendazole in a suitable basis that may contain suitable flavouring agents. Mebendazole chewable tablets contain not less than 90.0% and not more than 110.0% of the amount of mebendazole \((\text{C}_{16}\text{H}_{13}\text{N}_{3}\text{O}_{3})\) stated on the label.

Manufacture. The formulation, manufacturing process and product packaging of Mebendazole chewable 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, B and C or tests A, B and D 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. Shake a quantity of the powdered tablets containing 0.04 g of Mebendazole with 2 mL of sodium hydroxide (~80 g/L) TS and heat the yellowish coloured suspension; the solution is yellow. Add a few drops of copper (II) sulfate (160 g/L) TS; a greenish precipitate is produced. Add a few drops of ammonia (~100 g/L) TS; the colour of the precipitate turns to greenish blue.

C. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 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 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 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:

- mobile phase A: 7.5 g/L solution of ammonium acetate R;
- mobile phase B: Acetonitrile R.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Mobile phase A (%v/v)</th>
<th>Mobile phase B (%v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–15</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>
</tr>
<tr>
<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. 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 the solvent mixture, mix and filter. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL with the solvent mixture.

¹ A HYPERSIL BDS C₁₈ column has been found suitable.
Dilute 5.0 mL of this solution to 20.0 mL with the solvent mixture. For solution (3) transfer 10 mg mebendazole R 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\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 75% (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 cm × 4.6 mm) packed with octadecylsilyl base-deactivated silica gel for chromatography R (3 µm).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 (C₁₆H₁₃N₃O₃) in the chewable tablets using the declared content of C₁₆H₁₃N₃O₃ in mebendazole RS.

Impurities

The impurities limited by the requirements of this monograph includes impurity A listed in the monograph for Mebendazole.

Reagents to be established

Mebendazole R

Mebendazole of a suitable quality should be used.

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.
Methylthioninium chloride
(Methylthioninii chloridum)

This is a draft proposal of a monograph for The International Pharmacopoeia (Working document QAS/16.675, July 2016).

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: schmidt@who.int.

[Note from the Secretariat. It is proposed to revise the monograph on Methylthioninium chloride.]

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

Molecular formula. C_{16}H_{18}ClN_{3}S (anhydrous); C_{16}H_{18}ClN_{3}S\cdot H_2O (monohydrate);
C_{16}H_{18}ClN_{3}S\cdot 3H_2O (trihydrate); C_{16}H_{18}ClN_{3}S\cdot 5H_2O (pentahydrate).

Relative molecular mass. 319.9 (anhydrous); 337.9 (monohydrate); 373.9 (trihydrate); 409.9 (pentahydrate).

Graphic formula

\[
\begin{align*}
\text{H}_3\text{C} & \\
\text{N} & \\
\text{H} & \\
\text{N} & \\
\text{CH}_3 & \\
\text{Cl}^- & \\
\text{n H}_2\text{O} &
\end{align*}
\]

n=0 (anhydrous)
n=1 (monohydrate)
n=3 (trihydrate)
n=5 (pentahydrate)

Chemical name. C.I. Basic Blue 9; 3,7-bis(dimethylamino)phenothiazin-5-ium chloride; CAS Reg. No. 61-73-4 (anhydrous).

C.I. Basic Blue 9 monohydrate; 3,7-bis(dimethylamino)phenothiazin-5-ium chloride monohydrate; CAS Reg. No. 122965-43-9 (monohydrate).

C.I. Basic Blue 9 trihydrate; 3,7-bis(dimethylamino)phenothiazin-5-ium chloride trihydrate; CAS Reg. No. 7220-79-3 (trihydrate).

C.I. Basic Blue 9 pentahydrate; 3,7-bis(dimethylamino)phenothiazin-5-ium chloride pentahydrate; CAS Reg. No. 32680-41-4 (pentahydrate).

Other name. Methylene blue

Description. Dark green crystals with a metallic lustre or a dark green, crystalline powder.

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

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Category. Antidote.

Storage. Methylthioninium chloride should be kept in a tightly closed container, protected from light, at a temperature not exceeding 30°C.

Additional information. Methylthioninium chloride is hygroscopic.

Requirements

Definition. Methylthioninium chloride contains not less than 93.0% and not more than 102.0% (“Assay”, method A) or not less than 98.0% and not more than 102.0% (“Assay”, method B) of C_{16}H_{18}ClN_{3}S, calculated with reference to the dried substance.

Identity tests

• Either tests A and F or any two of tests B, C, D or E together with test F 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 methylthioninium chloride RS or with the reference spectrum of methylthioninium chloride.

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

C. The absorption spectrum (1.6) of a 5 μg/mL solution in hydrochloric acid (~70 g/L) TS, when observed between 230 nm and 800 nm, exhibits 4 maxima at about 258 nm, 288 nm, 680 nm, and 745 nm.

D. 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 3 volumes of acetic acid R, 3 volumes of ethanol R and 4 volumes of water R as the mobile phase. Apply separately to the plate 2 μL of each of the following 2 solutions in methanol R containing (A) 0.1 mg of the test substance per mL and (B) 0.1 mg of methylthioninium chloride RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of cool air. Examine the chromatogram in daylight.

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

E. Dissolve 1 mg in 10 mL of water R; a deep blue color is produced. Add 2.0 mL of hydrochloric acid (~70 g/L) TS and 0.25 g of zinc R powder; the color of the solution is discharged. Filter and expose the filtrate to the air; the blue color of the solution reappears.

F. Mix 0.05 g of the substance to be investigated with 0.5 g of anhydrous sodium carbonate R in a porcelain crucible. Carefully heat the mixture to a red glow for 10 minutes. Cool, dissolve the residue in 10 mL of nitric acid (~130 g/L) TS and filter. The filtrate yields reaction A described under 2.1 General identification tests as characteristic of chlorides.

Copper or zinc. Prepare the following solutions. For solution (1) ignite 1.0 g in a porcelain crucible using as low a temperature as practicable, until all of the carbon is oxidized. Cool the residue, add 15 mL of nitric acid (~130 g/L) TS and boil for 5 minutes. For solution (2) boil a quantity of copper(II) sulfate R, equivalent to 200 μg of Cu, with 15 mL of nitric acid (~130 g/L) TS for 5 minutes. Filter separately the cooled solutions (1) and (2) and wash any residue with 10 mL of water. Combine the filtrate and washings of the solution (1) and similarly combine the filtrate and washings of the solution (2); add to each an excess of ammonia (~100 g/L) TS
and filter the solutions into 50 mL volumetric flasks. Wash the precipitates with small portions of water, adding the washings to the filtrates; dilute the contents of each flask with water to volume, mixing thoroughly. To 25 mL of each of the solutions add 10 mL of hydrogen sulfide TS; no turbidity is produced within 5 minutes (absence of zinc) and any dark colour produced in solution (1) is not more intense than that of solution (2) (the copper content is not more than 0.20 mg/g).

**Iron.** Mix 4 g with 200 mL of water R in a long-necked, round-bottomed flask, add 15 mL of nitric acid (~1000 g/L) TS, heat carefully to boiling and continue boiling until the volume of liquid is reduced to about 20 mL. Allow to cool, add 10 mL of sulfuric acid (~1760 g/L) TS and mix. Heat to boiling and add small successive quantities of nitric acid (~1000 g/L) TS, cooling before each addition, until a colourless liquid is obtained. Heat until white fumes are evolved; if darkening occurs at this stage continue the treatment with nitric acid (~1000 g/L) TS. Finally heat until white fumes are again evolved. Allow the colourless liquid to cool, add 25 mL of a saturated solution of ammonium oxalate R in water, and boil until the slight froth completely subsides. Cool, dilute to 50 mL with water; 5 mL of the diluted solution complies with the 2.2.4 Limit test for iron; not more than 0.10 mg/g.

**Sulfated ash.** Not more than 2.5 mg/g.

**Loss on drying.** Dry at 105°C for 5 hours; it loses not more than 240 mg/g. (The dried substance may be used to produce solution (4) of the test “Related substances”).

**Related substances**

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

Prepare the following solutions using as the diluent a mixture of 70 volumes of a 0.1% (v/v) solution of trifluoroacetic acid R (mobile phase A) and 30 volumes of acetonitrile R (mobile phase B).

For solution (1) dissolve about 50 mg of the substance to be examined and dilute to 50.0 mL. Sonicate for 5 minutes. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3) dilute 5.0 mL of solution (2) to 50.0 mL. For solution (4) dissolve 2.5 mg methylthioninium chloride impurity A RS and dilute to 10.0 mL. Transfer 1.0 mL of this solution to a 10 mL volumetric flask and make up to volume with solution (1). Alternatively, dry the substance to be examined at 105°C for 5 h (the dried substance of the test “Loss on drying” may be used), dissolve 100 mg of the dried substance and dilute to 100.0 mL. Sonicate for 5 minutes.

Inject alternately 5 µL each of solutions (1), (2), (3), (4).

Use the chromatograms obtained with solution (4) and solution (1) to identify the peak due to impurity A. Impurity A is eluted at the relative retention of about 0.8 with reference to methylthioninium (retention time about 11 minutes). The test is not valid unless the resolution between the peaks corresponding to methylthioninium and impurity A is at least 3.5.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A is not greater than 5 times the area of the principal peak obtained with solution (2) (5.0%);
- the area of any other impurity peak is not greater than the area of the principal peak obtained with solution (3) (0.10%);
- the sum of the areas of all impurity peaks, other than the peak corresponding to impurity A, is not greater than 5 times the area of the principal peak obtained with solution (3) (0.5%). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (3) (0.05%).
Assay

- Either method A or B may be applied.

A. Carry out test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (10 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded phenylsilyl groups (3.5 µm).

Use the following conditions for gradient elution:

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>80</td>
<td>20</td>
<td>Isocratic</td>
</tr>
<tr>
<td>5–25</td>
<td>80 to 30</td>
<td>20 to 70</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>25–32</td>
<td>30</td>
<td>70</td>
<td>Isocratic</td>
</tr>
<tr>
<td>32–35</td>
<td>30 to 80</td>
<td>70 to 20</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>35–40</td>
<td>80</td>
<td>20</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate with a flow of 1.0 mL/min. As a detector use an ultraviolet spectrophotometer set at a wavelength of 246 nm. Maintain the column temperature at 30°C.

Prepare the following solutions using as diluent a mixture of 30 volumes of acetonitrile R and 70 volumes of mobile phase A. For solution (1) dissolve about 50 mg of the substance to be examined, accurately weighed, and dilute to 50.0 mL. Sonicate for 5 minutes. For solution (2) dissolve 50.0 mg of methylthioninium chloride RS and dilute to 50.0 mL. Sonicate for 5 min.

Inject alternately 5 µL each of solutions (1) and (2). The test is not valid unless the symmetry factor of methylthioninium is not more than 3.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of methylthioninium chloride (C₃₆H₃₈ClN₃S), using the declared content of C₃₆H₃₈ClN₃S in methylthioninium chloride RS.

B. Dissolve about 100 mg, accurately weighed, in sufficient ethanol (~457 g/L) TS to produce 250.0 mL. Dilute 5.0 mL of this solution to 100.0 mL with ethanol (~457 g/L) TS. Dilute 5.0 mL of this solution to 50.0 mL with ethanol (~457 g/L) TS. Measure the absorbance (1.6) of a 1 cm layer of the diluted solution at the maximum at about 664 nm and calculate the percentage content of methylthioninium chloride (C₃₆H₃₈ClN₃S) using the absorptivity value of 2950 methylthioninium chloride.

[Note from the Secretariat: The absorptivity value is so far based on a single determination. It is intended to perform further independent determinations to confirm the value.]

Additional requirements for Methylthioninium chloride for parenteral use

Complies with the monograph for Parenteral preparations.

Bacterial endotoxins. If intended for use in the manufacture of a parenteral dosage forms without a further appropriate procedure for the removal of bacterial endotoxins, carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 2.5 IU of endotoxin RS per mg.

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1 An X-Bridge Phenyl column and a Phenomenex Luna 3 µm Phenyl-Hexyl column were found suitable.
Impurities

A. 3-(Dimethylamino)-7-(methylamino)phenothiazin-5-i um chloride (azure B).

B. 3-Amino-7-(dimethylamino)phenothiazin-5-i um (azure A)

C. 3-amino-7-(methylamino)phenothiazin-5-i um (azure C)
Methylthioninium injection
(Methylthioninii injectio)

This is a draft proposal of a monograph for The International Pharmacopoeia (Working document QAS/16.676, July 2016).
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.

[Note from the Secretariat. The monograph is proposed for inclusion in The International Pharmacopoeia.]

Description. A clear, dark blue solution.

Category. Antidote

Storage. Store at room temperature, protected from light.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML): 10 mg/mL in 10 mL ampoule; other available strength: 5 mg/mL.

Requirements

Complies with the monograph for Parenteral preparations.

Definition. Methylthioninium injection is a sterile solution of Methylthioninium chloride in water for injection. It contains not less than 90.0% and not more than 110.0% of the amount of $C_{16}H_{18}ClN_3S$ stated on the label.

Identity tests

• Any two of tests A, B and C may be applied.

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

B. Carry out test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 3 volumes of acetic acid R, 3 volumes of ethanol R and 4 volumes of water R as the mobile phase. Apply separately to the plate 1 µL of each of the following 2 solutions: For solution (A) dilute 1.0 mL of the injection to 20.0 mL with methanol R to obtain a solution with a concentration of 0.5 mg of the methylthioninium chloride per mL. For solution (B) dissolve 10.0 mg of methylthioninium chloride RS and dilute to 20.0 mL with a mixture of water R and methanol R (20:80 v/v). After removing the plate from the chromatographic chamber allow it to dry in air or in a current of cool air. Examine the chromatogram in daylight.

The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).
C. The absorption spectrum (1.6) of a 5 µg/mL solution in hydrochloric acid (~70 g/L) TS, when observed between 230 nm and 800 nm, exhibits 4 maxima at about 258 nm, 288 nm, 680 nm and 745 nm.

pH value (1.13). pH of the injection, 3.0–4.5

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

Prepare the following solutions using as the diluent a mixture of 70 volumes of a 0.1% (v/v) solution of trifluoroacetic acid R (mobile phase A) and 30 volumes of acetonitrile R (mobile phase B).

For solution (1) dilute 1.0 mL of the injection to 20.0 mL to obtain a solution with a concentration of 0.5 mg of the methylthioninium chloride per mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3) dilute 5.0 mL of solution (2) to 50.0 mL. For solution (4) dissolve 2.5 mg methylthioninium chloride impurity A RS and dilute to 10.0 mL. Transfer 1.0 mL of this solution to a 10 mL volumetric flask and make up to volume with solution (1). Alternatively, dry 100 mg of methylthioninium chloride R at 105°C for 5 hours, dissolve 50 mg of the dried substance and dilute to 100.0 mL. Sonicate for 5 minutes.

Inject alternately 5 µL each of solutions (1), (2), (3) and (4).

Use the chromatograms obtained with solution (4) and solution (1) to identify the peak due to impurity A. Impurity A is eluted at the relative retention of about 0.8 with reference to methylthioninium (retention time about 11 minutes). The test is not valid unless the resolution between the peaks corresponding to methylthioninium and impurity A is at least 3.5.

In the chromatogram obtained with solution (1):

• the area of any peak corresponding to impurity A is not greater than 5 times the area of the principal peak obtained with solution (2) (5.0%);

• the area of any other impurity peak is not greater than two times the area of the principal peak obtained with solution (3) (0.20%);

• the sum of the areas of all impurity peaks, other than the peak corresponding to impurity A, is not greater than the area of the principal peak obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.5 times the area of the principal peak obtained with solution (3) (0.05%).

Assay
• Either method A or B may be applied.

A. Carry out test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (10 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded phenylsilyl groups (3.5 µm).

Use the following conditions for gradient elution:

- mobile phase A: 0.1 % (v/v) solution of trifluoroacetic acid R;
- mobile phase B: acetonitrile R.

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1 An X-Bridge Phenyl column and a Phenomenex Luna 3 µm Phenyl-Hexyl column were found suitable.
**Time (minutes)** | **Mobile phase A (% v/v)** | **Mobile phase B (% v/v)** | **Comments**
---|---|---|---
0–5 | 80 | 20 | Isocratic
5–25 | 80 to 30 | 20 to 70 | Linear gradient
25–32 | 30 | 70 | Isocratic
32–35 | 30 to 80 | 70 to 20 | Return to initial composition
35–40 | 80 | 20 | Re-equilibration

Operate with a flow of 1.0 mL/min. As a detector use an ultraviolet spectrophotometer set at a wavelength of 246 nm. Maintain the column temperature at 30°C.

Prepare the following solutions using as dilutent a mixture of 30 volumes acetonitrile R and 70 volumes of mobile phase A. For solution (1) dilute 5.0 mL of the injection to 50.0 mL. Dilute 5.0 mL of this solution to 50.0 mL to obtain a solution with a concentration of 0.1 mg of methylthioninium chloride per mL. For solution (2) dissolve 50.0 mg of methylthioninium chloride RS in 50.0 mL. Sonicate for 5 minutes. Dilute 5.0 mL of this solution to 50.0 mL.

Inject alternately 5 µL each of solutions (1) and (2). The test is not valid unless symmetry factor is not more than 2.0.

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of methylthioninium chloride \((\text{C}_{16}\text{H}_{18}\text{ClN}_{3}\text{S})\) using the declared content of \(\text{C}_{16}\text{H}_{18}\text{ClN}_{3}\text{S}\) in methylthioninium chloride RS.

B. Prepare the following solutions using as diluent ethanol (~457 g/L) TS. Dilute 1.0 mL of the injection to 100.0 mL to obtain a solution with a concentration of 0.1 mg of methylthioninium chloride per mL. Dilute 2.0 mL of this solution to 100.0 mL. Measure the absorbance \((1.6)\) of a 1 cm layer of the diluted solution at the maximum at about 664 nm and calculate the percentage content of methylthioninium chloride \((\text{C}_{16}\text{H}_{18}\text{ClN}_{3}\text{S})\) using the absorptivity value of 2950 methylthioninium chloride.

**[Note from the Secretariat. The absorptivity value is so far based on a single determination. It is intended to perform further independent determinations to confirm the value.]**

**Bacterial endotoxins.** Carry out the test as described under 3.4 **Test for bacterial endotoxins;** contains less than 2.5 IU of endotoxin per mg methylthioninium chloride.

**Impurities**

The impurities limited by the requirements of this monograph include those listed in the monograph for methylthioninium chloride.

**Reagent to be established**

**Methylthioninium chloride R**

Methylthioninium chloride of a suitable quality should be used.

***
Proposed revision of the general chapter
1.11 Colour of liquids

This is a proposed revision of the general chapter 1.11 Colour of liquids for The International Pharmacopoeia (Working document QAS/16.659, July 2016).

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.

[Note from the Secretariat.]

Addition of the test Degree of coloration of liquids (1.11.2), reproduced from the European Pharmacopoeia

In the current procedure for the preparation of the four colour stock standard test solutions used in chapter 1.11 Colour of liquid (yellow stock standard TS, red stock standard TS, green stock standard TS and brown stock standard TS) dichromate colour TS is used.

In order to replace chromium (VI) salts it is propose to gradually replace the existing procedure with the one used in the European Pharmacopoeia. (The permission to reproduce the procedure will be requested when the proposed text is adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations).

For the period of transition, the original text shall be kept under the section 1.11.1; the new test procedure shall be added under the section 1.11.2.

With the publication of the proposed revision of chapter 1.11 Colour of liquid, references to this chapter in existing monographs will be replaced with the reference to chapter 1.11.1. In new and revised monographs the new test procedure 1.11.2 will be applied.

The definition of “colourless” under General Notices

In the section General Notices a colourless solution is defined by referring to chapter 1.11 Colour of liquids as follows:

“A solution is considered colourless if it is not more intensely coloured than any of the standard colour solutions Bn0, Yw0, Gn0, or Rd0. The matching is made with the solution of most appropriate hue as described under 1.11 Colour of liquids.”

The specification colourless is mostly used in the sections “Clarity and colour of solution” of monographs, with and without explicit reference to chapter 1.11 Colour of liquids.

For the sake of clarity, it is proposed to delete the definition of “colourless” under General Notes and to put the definition of “colourless” under 1.11.1. Those specifications under “clarity and colour of solution” that currently do not refer to chapter 1.11 Colour of liquids are to be supplemented by a respective reference.]

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

1.11 Colour of liquid

In order to replace chromium (VI) salts in The International Pharmacopoeia the procedure previously used to determine the colour of liquids will be replaced gradually with the corresponding procedure taken over from the European Pharmacopoeia.

For the period of transition, both procedures are kept: the previous procedure under section 1.11.1 and the new procedure under section 1.11.2.
1.11.1 Colour of liquids

The test for colour of liquids is carried out by comparing the test solution prepared as specified in the monograph with a standard colour solution indicated in the monograph. The composition of the standard colour solution is selected depending on the hue and intensity of the colour of the test solution corresponding to the limits permitted in the specifications.

**Recommended procedure**

Unless otherwise specified in the monograph, carry out the comparison in flat-bottomed tubes of transparent glass that are matched as closely as possible in internal diameter and in all other respects (tubes of about 16 mm internal diameter are suitable). Use 10 mL of the test solution and 10 mL of the standard colour solution; the depth of liquid should be about 50 mm. The colour of the test solution is not more intense than the standard colour when viewed down the vertical axis of the tubes in diffused light against a white background.

**Stock colour standard solutions**

**Yellow stock standard TS**

To 9.5 mL of cobalt colour TS, add 1.9 mL of copper colour TS, 10.7 mL of dichromate colour TS, 4.0 mL of iron colour TS, dilute to 100.0 mL with sulfuric acid (~10 g/L) TS and mix.

**Red stock standard TS**

To 40.5 mL of cobalt colour TS, add 6.1 mL of copper colour TS, 6.3 mL of dichromate colour TS, 12.0 mL of iron colour TS, dilute to 100.0 mL with sulfuric acid (~10 g/L) TS and mix.

**Green stock standard TS**

To 3.5 mL of cobalt colour TS, add 20.1 mL of copper colour TS, 10.4 mL of dichromate colour TS, 4.0 mL of iron colour TS, dilute to 100.0 mL with sulfuric acid (~10 g/L) TS and mix.

**Brown stock standard TS**

To 35.0 mL of cobalt colour TS, add 17.0 mL of copper colour TS, 8.0 mL of dichromate colour TS, dilute to 100.0 mL with iron colour TS and mix.

**Standard colour solutions**

The standard colour solution is prepared by suitably diluting the stock standard solutions (yellow, red, green and brown stock standard TS) with sulfuric acid (~10 g/L) TS. The designation of the standard colour solution is composed of two letters indicating the stock standard solution (Yw for yellow, Rd for red, Gn for green and Bn for brown) and of a number describing the dilution as given below:

<table>
<thead>
<tr>
<th>Dilution number for standard colour solutions</th>
<th>Stock standard solution (mL)</th>
<th>Sulfuric acid (~10g/L) TS (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.78</td>
<td>99.22</td>
</tr>
<tr>
<td>1</td>
<td>1.56</td>
<td>98.44</td>
</tr>
<tr>
<td>2</td>
<td>3.12</td>
<td>96.88</td>
</tr>
<tr>
<td>3</td>
<td>6.25</td>
<td>93.75</td>
</tr>
<tr>
<td>4</td>
<td>12.50</td>
<td>87.50</td>
</tr>
<tr>
<td>5</td>
<td>25.00</td>
<td>75.00</td>
</tr>
<tr>
<td>6</td>
<td>50.00</td>
<td>50.00</td>
</tr>
<tr>
<td>7</td>
<td>100.00</td>
<td>-</td>
</tr>
</tbody>
</table>

Standard colour solution numbers 4–7 may be stored in sealed glass containers, protected from sunlight but the more dilute standard colour solutions should be prepared as required.
Definition of “colourless”
A solution is considered colourless if it is not more intensely coloured than any of the standard colour solutions Bn0, Yw0, Gn0 or Rd0.

1.11.2 Degree of colouration of liquids

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[Note from the Secretariat. The permission will be requested when the text is adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations.]

The examination of the degree of coloration of liquids in the range brown-yellow-red is carried out by one of the 2 methods below as prescribed in the monograph.

A solution is colourless if it has the appearance of water R or the solvent or is not more intensely coloured than reference solution B9.

METHOD I
Using identical tubes of colourless, transparent, neutral glass of 12 mm external diameter, compare 2.0 mL of the liquid to be examined with 2.0 mL of water R or of the solvent or of the reference solution (see tables of reference solutions) prescribed in the monograph. Compare the colours in diffused daylight, viewing horizontally against a white background.

METHOD II
Using identical tubes of colourless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm, compare the liquid to be examined with water R or the solvent or the reference solution (see tables of reference solutions) prescribed in the monograph, the depth of the layer being 40 mm. Compare the colours in diffused daylight, viewing vertically against a white background.

REAGENTS

Primary solutions

Yellow solution. Dissolve 46 g of ferric chloride R in about 900 mL of a mixture of 25 mL of hydrochloric acid (~330 g/L) TS and 975 mL of water R and dilute to 1000.0 mL with the same mixture. Titrate and adjust the solution to contain 45.0 mg of FeCl₃·6H₂O per mL by adding the same acidic mixture. Protect the solution from light.

Titration. Place in a 250 mL conical flask fitted with a ground-glass stopper, 10.0 mL of the solution, 15 mL of water R, 5 mL of hydrochloric acid (~330 g/L) TS and 4 g of potassium iodide R, close the flask, allow to stand in the dark for 15 minutes and add 100 mL of water R. Titrate the liberated iodine with sodium thiosulfate (0.1 mol/L) VS, using 0.5 mL of starch solution TS, added towards the end of the titration, as indicator.

1 mL of sodium thiosulfate (0.1 mol/L) VS is equivalent to 27.03 mg of FeCl₃·6H₂O.

Red solution. Dissolve 60 g of cobalt (II) chloride R in about 900 mL of a mixture of 25 mL of hydrochloric acid (~330 g/L) TS and 975 mL of water R and dilute to 1000.0 mL with the same mixture. Titrate and adjust the solution to contain 59.5 mg of CoCl₂·6H₂O per mL by adding the same acidic mixture.
Titration. Place in a 250 mL conical flask fitted with a ground-glass stopper, 5.0 mL of the solution, 5 mL of hydrogen peroxide (~30 g/L) TS and 10 mL of sodium hydroxide (~300 g/L) TS. Boil gently for 10 minutes, allow to cool and add 60 mL of sulfuric acid (~100 g/L) TS and 2 g of potassium iodide R. Close the flask and dissolve the precipitate by shaking gently. Titrate the liberated iodine with sodium thiosulfate (0.1 mol/L) VS, using 0.5 mL of starch solution TS, added towards the end of the titration, as indicator. The end-point is reached when the solution turns pink.

1 mL of sodium thiosulfate (0.1 mol/L) VS is equivalent to 23.79 mg of CoCl\(_2\)\(\cdot6\)H\(_2\)O.

*Blue solution.* Dissolve 63 g of copper (II) sulfate R in about 900 mL of a mixture of 25 mL of hydrochloric acid (~330 g/L) TS and 975 mL of water R and dilute to 1000.0 mL with the same mixture. Titrate and adjust the solution to contain 62.4 mg of CuSO\(_4\)\(\cdot5\)H\(_2\)O per mL by adding the same acidic mixture.

Titration. Place in a 250 mL conical flask fitted with a ground-glass stopper, 10.0 mL of the solution, 50 mL of water R, 12 mL of acetic acid (~120 g/L) TS and 3 g of potassium iodide R. Titrate the liberated iodine with sodium thiosulfate (0.1 mol/L) VS, using 0.5 mL of starch solution TS, added towards the end of the titration, as indicator. The end-point is reached when the solution shows a slight pale brown colour.

1 mL of sodium thiosulfate (0.1 mol/L) VS is equivalent to 24.97 mg of CuSO\(_4\)\(\cdot5\)H\(_2\)O.

**Standard solutions**

Using the 3 primary solutions, prepare the 5 standard solutions as follows (*Table 1*).

*Table 1. Standard solutions*

<table>
<thead>
<tr>
<th>Standard solution</th>
<th>Volumes in mL</th>
<th>Hydrochloric acid (~10 g/L) TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BY (brownish-yellow)</td>
<td>2.4, 1.0, 0.4</td>
<td>6.2</td>
</tr>
<tr>
<td>Y (yellow)</td>
<td>2.4, 0.6, 0.0</td>
<td>7.0</td>
</tr>
<tr>
<td>GY (greenish-yellow)</td>
<td>9.6, 0.2, 0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>R (red)</td>
<td>1.0, 2.0, 0.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

**Reference solutions for Methods I and II**

Using the 5 standard solutions, prepare the following reference solutions.

*Table 2. Reference solutions B*

<table>
<thead>
<tr>
<th>Reference solution</th>
<th>Volumes in mL</th>
<th>Hydrochloric acid (~10 g/L) TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>B(_1)</td>
<td>75.0</td>
<td>25.0</td>
</tr>
<tr>
<td>B(_2)</td>
<td>50.0</td>
<td>50.0</td>
</tr>
<tr>
<td>B(_3)</td>
<td>37.5</td>
<td>62.5</td>
</tr>
<tr>
<td>B(_4)</td>
<td>25.0</td>
<td>75.0</td>
</tr>
<tr>
<td>B(_5)</td>
<td>12.5</td>
<td>87.5</td>
</tr>
<tr>
<td>B(_6)</td>
<td>5.0</td>
<td>95.0</td>
</tr>
<tr>
<td>B(_7)</td>
<td>2.5</td>
<td>97.5</td>
</tr>
<tr>
<td>B(_8)</td>
<td>1.5</td>
<td>98.5</td>
</tr>
<tr>
<td>B(_9)</td>
<td>1.0</td>
<td>99.0</td>
</tr>
</tbody>
</table>
### Table 3. Reference solutions BY

<table>
<thead>
<tr>
<th>Reference solution</th>
<th>Volumes in mL</th>
<th>Standard solution BY</th>
<th>Hydrochloric acid (~10 g/L) TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BY1</td>
<td>100.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>BY2</td>
<td>75.0</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>BY3</td>
<td>50.0</td>
<td>50.0</td>
<td></td>
</tr>
<tr>
<td>BY4</td>
<td>25.0</td>
<td>75.0</td>
<td></td>
</tr>
<tr>
<td>BY5</td>
<td>12.5</td>
<td>87.5</td>
<td></td>
</tr>
<tr>
<td>BY6</td>
<td>5.0</td>
<td>95.0</td>
<td></td>
</tr>
<tr>
<td>BY7</td>
<td>2.5</td>
<td>97.5</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Reference solutions Y

<table>
<thead>
<tr>
<th>Reference solution</th>
<th>Volumes in mL</th>
<th>Standard solution Y</th>
<th>Hydrochloric acid (~10 g/L) TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y1</td>
<td>100.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Y2</td>
<td>75.0</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Y3</td>
<td>50.0</td>
<td>50.0</td>
<td></td>
</tr>
<tr>
<td>Y4</td>
<td>25.0</td>
<td>75.0</td>
<td></td>
</tr>
<tr>
<td>Y5</td>
<td>12.5</td>
<td>87.5</td>
<td></td>
</tr>
<tr>
<td>Y6</td>
<td>5.0</td>
<td>95.0</td>
<td></td>
</tr>
<tr>
<td>Y7</td>
<td>2.5</td>
<td>97.5</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5. Reference solutions GY

<table>
<thead>
<tr>
<th>Reference solution</th>
<th>Volumes in mL</th>
<th>Standard solution GY</th>
<th>Hydrochloric acid (~10 g/L) TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GY1</td>
<td>25.0</td>
<td>75.0</td>
<td></td>
</tr>
<tr>
<td>GY2</td>
<td>15.0</td>
<td>85.0</td>
<td></td>
</tr>
<tr>
<td>GY3</td>
<td>8.5</td>
<td>91.5</td>
<td></td>
</tr>
<tr>
<td>GY4</td>
<td>5.0</td>
<td>95.0</td>
<td></td>
</tr>
<tr>
<td>GY5</td>
<td>3.0</td>
<td>97.0</td>
<td></td>
</tr>
<tr>
<td>GY6</td>
<td>1.5</td>
<td>98.5</td>
<td></td>
</tr>
<tr>
<td>GY7</td>
<td>0.75</td>
<td>99.25</td>
<td></td>
</tr>
</tbody>
</table>

### Table 6. Reference solutions R

<table>
<thead>
<tr>
<th>Reference solution</th>
<th>Volumes in mL</th>
<th>Standard solution R</th>
<th>Hydrochloric acid (~10 g/L) TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>100.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>R2</td>
<td>75.0</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>R3</td>
<td>50.0</td>
<td>50.0</td>
<td></td>
</tr>
<tr>
<td>R4</td>
<td>37.5</td>
<td>62.5</td>
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</tr>
<tr>
<td>R5</td>
<td>25.0</td>
<td>75.0</td>
<td></td>
</tr>
<tr>
<td>R6</td>
<td>12.5</td>
<td>87.5</td>
<td></td>
</tr>
<tr>
<td>R7</td>
<td>5.0</td>
<td>95.0</td>
<td></td>
</tr>
</tbody>
</table>
Storage

For Method I the reference solutions may be stored in sealed tubes of colourless, transparent, neutral glass of 12 mm external diameter, protected from light.

For Method II prepare the reference solutions immediately before use from the standard solutions.

Reagents to be established

Starch solution TS

Triturate 1.0 g of soluble starch R with 5 mL of water R and whilst stirring pour the mixture into 100 mL of boiling water R containing 10 mg of mercuric iodide R.

NOTE: commercially available reagents may be used; including mercury-free solutions or those containing alternative preservatives.

Carry out the test for sensitivity each time the reagent is used.

Test for sensitivity. To a mixture of 1 mL of the starch solution and 20 mL of water R, add about 50 mg of potassium iodide R and 0.05 mL of iodine solution TS. The solution is blue.

Hydrogen peroxide (~30 g/L) TS

A solution in water containing about 30 g of H2O2 per litre.

Hydrochloric acid (~10 g/L) TS

Hydrochloric acid (~250 g/L) TS, dilute with water to contain 10 g of HCl in 1000 mL.

Iodine solution TS

To 10.0 mL of M iodine (0.05 mol/L)VS add 0.6 g of potassium iodide R and dilute to 100.0 mL with water R. Prepare immediately before use.

***