WHO Drug Information

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<th>Description</th>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use (EMA)</td>
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<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration (<a href="http://www.fda.gov">www.fda.gov</a>)</td>
</tr>
<tr>
<td>Health Canada</td>
<td>Federal department responsible for health product regulation in Canada (<a href="http://www.hc-sc.gc.ca">www.hc-sc.gc.ca</a>)</td>
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<tr>
<td>IGDRP</td>
<td>International Generic Drug Regulators Programme (<a href="https://www.igdrp.com">https://www.igdrp.com</a>)</td>
</tr>
<tr>
<td>MHLW</td>
<td>Ministry of Health, Labour and Welfare, Japan</td>
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<tr>
<td>MHRA</td>
<td>Medicines and Healthcare Products Regulatory Agency, United Kingdom (<a href="http://www.mhra.gov.uk">www.mhra.gov.uk</a>)</td>
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<tr>
<td>Medsafe</td>
<td>New Zealand Medicines and Medical Devices Safety Authority (<a href="http://www.medsafe.govt.nz">www.medsafe.govt.nz</a>)</td>
</tr>
<tr>
<td>PRAC</td>
<td>Pharmacovigilance Risk Assessment Committee (EMA)</td>
</tr>
<tr>
<td>PMDA</td>
<td>Pharmaceuticals and Medical Devices Agency, Japan (<a href="http://www.pmda.go.jp/english/index.htm">www.pmda.go.jp/english/index.htm</a>)</td>
</tr>
<tr>
<td>Swissmedic</td>
<td>Swiss Agency for Therapeutic Products (<a href="http://www.swissmedic.ch">www.swissmedic.ch</a>)</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration, Australia (<a href="http://www.tga.gov.au">www.tga.gov.au</a>)</td>
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<tr>
<td>U.S.</td>
<td>United States of America</td>
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<tr>
<td>WHO</td>
<td>World Health Organization (<a href="http://www.who.int">www.who.int</a>)</td>
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<tr>
<td>WHO PQT</td>
<td>WHO Prequalification team (<a href="https://extranet.who.int/prequal/">https://extranet.who.int/prequal/</a>)</td>
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**Note:**
The online version of this issue (freely available at [www.who.int/medicines/publications/druginformation](http://www.who.int/medicines/publications/druginformation)) has direct clickable hyperlinks to the documents and web pages referenced.
Collaboration

Global network of national vaccine control laboratories

Immunization is one of the most cost-effective public health interventions. However, vaccines are complex biological products that need comprehensive regulatory oversight, including control of each lot released onto the market. For WHO-prequalified vaccines, lot release is under the responsibility of the authority with the regulatory oversight of the respective vaccine, which is usually the national regulatory authority (NRA) of the producing country.

Lot release testing of vaccines is becoming more demanding and resource-intensive as globalization and scientific advances progress, making it necessary for national control laboratories (NCLs) to collaborate in order to ensure the timely supply of quality-assured vaccines to countries. With this in mind, WHO has brought together representatives of NCLs involved in testing of WHO-prequalified vaccines, industry and other stakeholders to explore the potential for more extensive sharing of work and information. A network of NCLs responsible for release of WHO-prequalified vaccines was established.

Background

Assuring the quality of vaccines
Ensuring the consistent safety and efficacy of vaccines is critical for the success of immunization programmes. It is also essential for continued public confidence in these programmes, enabling adequate immunization coverage to be achieved and maintained.

To facilitate access to needed vaccines of assured quality the WHO Prequalification Team (PQT) prequalifies vaccines for procurement by UN agencies according to a defined procedure (1). The outcomes are also used by governments and international organizations.

Vaccines are complex biological products with inherent variability between produced batches. A prerequisite for acceptance of applications for WHO prequalification is,
therefore, that the regulatory authority of the producing country is proven functional with regard to regulatory oversight of vaccines. Two of the nine common functions assessed by WHO\(^1\) are the access to a functional vaccine control laboratory and the ability to perform lot release, including risk-based laboratory testing, to confirm that each batch meets the specifications of its marketing authorization before it is released onto the market. This regulatory function, NRA lot release, is unique to vaccines and a few other biological products.

For WHO-prequalified vaccines intended for use in UN-funded programmes, lot release is conducted in accordance with WHO guidelines\(^2\) by the NRA of the producing country as the responsible authority. In addition, the WHO Technical Assistance and Laboratory Services (TAL) Group coordinates the testing of vaccines submitted for prequalification (verification of quality in support of prequalification decision) and the targeted testing, by WHO-contracted NCLs\(^2\), of vaccine lots supplied to countries by UN agencies.

**WHO collaborative activities**

With increasing globalization and continuous scientific advances, quality assurance of vaccines is becoming more demanding. Challenges with regard to lot release of vaccines were discussed at a 2007 WHO/Health Canada consultation\(^{3}\), where it was noted that the increased volume of vaccines being licensed and in use, the increasing complexity of new vaccines requiring more sophisticated tests and the increasing globalization of vaccine production created an increasing burden for NRAs and industry.

In response to these challenges WHO-PQT has initiated a range of activities to promote collaboration and work-sharing. A streamlined vaccine prequalification procedure\(^{1}\) was introduced with effect from February 2012, allowing for case-by-case reliance on assessment reports, testing results and/or inspection reports shared by NRAs under specific collaboration agreements. To increase the efficiency of testing WHO-TAL has increased the number of its contracted laboratories, optimized the testing logistics, and invested in harmonization of test methodologies with hands-on training courses and information exchange\(^{4}\). Since 2014, 16 agreements have been signed with manufacturers of prequalified vaccines, allowing the releasing NCLs to share the data gathered during their independent national lot release as part of their annual reporting to WHO.

**First global network meeting**

Building on these collaborative activities, WHO-TAL initiated and coordinated a first kick-off networking meeting to create a strategic platform for NCLs to collaborate and share information. The meeting was jointly organized with the Dutch National Institute for Public Health and the Environment (RIVM). Representatives from national laboratories involved in testing WHO-prequalified vaccines are invited to join the meeting to further consider the establishment of a global network of NCLs.

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\(^1\) The nine common functions are defined in the WHO Global Benchmarking Tool, which is being phased in. They are:
1. National regulatory system;
2. Registration and marketing authorization;
3. Vigilance;
4. Market surveillance and control;
5. Licensing premises;
6. Regulatory inspection;
7. Laboratory access and testing;
8. Clinical trials oversight; and
9. NRA lot release.

\(^2\) A list of contracted laboratories is available on the WHO website at [www.who.int/immunization_standards/vaccine_quality/contracted_labs_vaccines/en/](http://www.who.int/immunization_standards/vaccine_quality/contracted_labs_vaccines/en/)
vaccines, industry associations and other stakeholders met on 30 August–2 September 2016 in Lage Vuursche, the Netherlands, to exchange information on their vaccine control strategies and explore opportunities to promote convergence. This was the first meeting of national vaccine control laboratories that had a global reach, with participation from NCLs in five of the six WHO regions (Table 1).

### Lot release activities

The laboratory representatives described the lot release activities performed at their institutions. The number of batches released per year at each NCL ranged from just over 100 to several thousand; an increasing trend was reported from several countries. All laboratories reported that they work according to ISO 17025 standards. Most were accredited, one had an audit-based system and one was working towards accreditation. All laboratories reported being engaged in international and regional collaboration initiatives; collaborative studies and joint audits were highlighted as being particularly useful exercises.

### Lot release procedures

Review of the lot summary protocol was part of the lot release procedure in all countries. For imported vaccines there was some reliance on the lot release by the responsible regulatory authorities in producing countries, particularly those affiliated to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Some laboratories reported using different release certificates for the domestic market and for export, while others stated that they use the same testing schedules for all samples, as they do not know which samples are intended for export.
Although all laboratories released batches of UN-procured vaccines according to WHO lot testing guidelines (2), it turned out that the actual lot release practices differed:

- The decision to test was risk-based in most countries, even where regulations require testing of all batches, as is the case in the EU and South Africa. In the Republic of Korea a risk-based system was introduced in April 2016. On the other hand, all batches of finished product and of drug substance are tested in the United Kingdom. Likewise, all batches are tested in Japan in line with public expectations; efforts are under way towards introducing a risk-based approach.

- The selection of lots for testing was based on the nature of the product and other factors such as consistency of production, product history – including inspection findings, complaints, adverse events following immunization (AEFI) – and change control. Some laboratories reported that they do not perform any testing at all for specific products which have been categorized as being of low risk.

- Where testing was performed, the percentage of lots tested ranged from 10% (or at least three lots per year) to 100% of batches released.

- The parameters tested were found to differ between countries. While some laboratories perform the full range of release tests in accordance with the manufacturer’s marketing authorization, the relevant WHO guideline or the pharmacopoeial monograph, others select critical parameters for testing based on the nature of the product and the laboratory’s technical capabilities. It was noted that certain tests, such as that for potency at the final bulk stage, can be performed in parallel with manufacturers’ tests to save time.

Manufacturers’ perspective

Representatives of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and the Developing Countries Vaccine Manufacturers Network (DCVM) shared the manufacturers’ perspective. Manufacturers recognize the public health benefits of the independent lot release process and share the common goal to ensure timely availability of safe, efficacious and high quality vaccines.

Some prequalified vaccines are supplied to over 100 countries. Target countries have diverse national regulatory requirements, and many have requirements for full release testing of vaccine lots. Re-testing of the same batch in four or more recipient countries was said to be not uncommon. Often the testing provides no added value and can pose a risk of out-of-specification results that are not linked to actual product deficiencies. This creates significant barriers for manufacturers in supplying vaccines to end users.

In light of current regulatory developments, notably the move towards risk management and quality by design concepts, manufacturers are calling for risk-based testing as recommended in WHO guidelines (2) and for more reliance on the testing results of the competent authority in charge of the regulatory oversight of the product. The need for convergence of lot release requirements as a basis for information- and work-sharing was emphasized.

Discussions and outcomes

Best practice for lot release

The meeting participants noted that lot release is only one element of a more comprehensive oversight that includes a range of regulatory mechanisms such as licensing activities, market surveillance and
inspection of production sites. They voiced their support for a move towards risk-based selection of lots and parameters for testing. It was further emphasized that unexpected findings in lot release testing should be investigated in close consultation with manufacturers.

There was general agreement that the same requirements should apply for vaccines released onto the local market and those for export, and that reliance on the batch release by the responsible NRA/NCL (usually that of the producing country) should be promoted.

Participants felt that a gradual convergence of lot release practices in line with WHO guidance (2) can be achieved by incorporating best practices into national guidelines. As a first step, the participating NCLs agreed to conduct a mapping exercise of the processes used in lot release of WHO-prequalified and other vaccines to complement the information that was shared during the meeting.

**Lot release certificate**

Regulatory authorities/NCLs are required to issue a certificate of release for all lots of vaccines, including the prequalified vaccines that are distributed through United Nations agencies. An example (5) was reviewed at the meeting. A revised model template was proposed that can be used for all types of WHO-prequalified vaccines (Appendix 1).

The proposed template includes a reference to Paragraph 7.3 of the WHO lot release guideline, which describes the role of lot release in the context of comprehensive regulatory oversight (Box 1), and mentions ISO 17025 as the common standard followed by the participating laboratories.

**Information-sharing**

The meeting participants considered various mechanisms to increase information-sharing among laboratories involved in testing of WHO-prequalified vaccines. It was proposed to adopt a structured, step-wise approach to information-sharing on an “as-needed” basis in consultation with manufacturers and with due arrangements to ensure confidentiality.

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**Box 1: Vaccine lot release in the context of comprehensive regulatory oversight**

From: WHO lot release guidelines (2), Paragraph 7.3:

“The responsible national regulatory agencies (NRAs)/national control laboratories (NCLs) are required to issue a certificate of release for vaccines that are distributed through United Nations agencies. Vaccines distributed through United Nations agencies are prequalified by WHO, to ensure that the products comply with the quality and safety standards established by the Organization. This release certificate is issued on the basis of, as a minimum, a review of the lot summary protocol for the relevant lot.

The responsible NRA/NCL plays a key role in ensuring that products meet the specifications outlined in the marketing authorization and WHO recommendations. This is achieved by maintaining regulatory oversight, assessing and approving changes to manufacturing processes – including testing and specifications, compliance with good manufacturing practices (GMP) – and post-marketing surveillance of adverse events following immunization (AEFI). The release certificate issued by the responsible NRA/NCL should be forwarded by the United Nations agencies to the NRA/NCL of the receiving country, and the summary protocol will be provided upon request.”

Global network of national vaccine control laboratories
The meeting itself was recognized as a starting point for this information-sharing as it established a common platform and provided a first overview of the participating NCLs’ strategies for vaccine control. By the end of 2017, shareable information could include the numbers of vaccine lots released as well as information relating to the laboratory testing, such as the risk-based considerations underlying the testing schedules. In the medium and long term, laboratories may go on to share lot release results and comparisons with manufacturer’s results, lot release certificates, and information on testing methodologies. The establishment of a secure and user-friendly electronic platform with access rights management for different user types will be considered.

Network of vaccine control laboratories
The meeting participants agreed to form a network of NCLs responsible for testing of WHO-prequalified vaccines, with the main objectives to promote information-sharing and convergence of lot release practices. The network may also serve to promote the “3R” principles – reducing, refining and replacing animal testing – as a means to make testing less variable and thus more efficient without compromising vaccine quality.

Draft terms of reference and management principles were agreed as follows at the meeting: Membership in the network is voluntary but strongly encouraged, and will be confirmed by the participating NCLs after the meeting. NCLs in countries that are recipients of UN-procured vaccines can join as associate members, while industry and other stakeholders can participate as observers.

An interim steering committee was appointed at the meeting. The first regular steering committee will be elected at the next network meeting, which is planned to take place in India in the second half of 2017.

Conclusions
With 194 Member States worldwide, WHO has a mandate to coordinate a strategic vaccine control laboratory network at the global level. The network established at the meeting has the potential to promote collaboration and reliance around the globe, considering that WHO-prequalified vaccines are used to immunize approximately two thirds of infants worldwide (6). The newly formed network will communicate its experience “upward”, providing input to WHO and national guidance to promote convergence of lot release practices, and “outward” to countries receiving WHO-prequalified vaccines in order to raise awareness and foster reliance on the release testing conducted by the network members. The potential benefits are significant. Convergence of lot release requirements and test protocols and minimization of redundant testing will help to increase access to quality-assured vaccines in WHO Member States, thus supporting the achievement of universal health coverage which is one of the targets in the United Nations’ health-related sustainable development goals.

References


Global network of national vaccine control laboratories

Appendix 1: Proposed revised model lot release certificate

Model certificate for the release of prequalified vaccines by NRAs

<table>
<thead>
<tr>
<th>Lot-release certificate</th>
<th>Certificate no. ........ (to be repeated on each page)</th>
</tr>
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<tbody>
<tr>
<td>The following lot(s) of ........ vaccine produced by .........., whose numbers appear on the labels of the final evaluated containers, complies with the relevant marketing authorization, the national specifications and provisions for the release of biological products and Part A of the WHO Recommendations to assure the quality, safety and efficacy of the concerned vaccines (yyyy), and with corresponding WHO recommendations for each of the vaccine’s individual components, as well as with WHO good manufacturing practices: main principles for pharmaceutical products; Good manufacturing practices for biological products; and Guidelines for independent lot release of vaccines by regulatory authorities.</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Trade name:</th>
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<tbody>
<tr>
<td>International non-proprietary Name / Common name:</td>
<td></td>
</tr>
<tr>
<td>Batch numbers appearing on package and other identification numbers associated with this batch:*</td>
<td></td>
</tr>
<tr>
<td>* Such as batch number on final bulk</td>
<td></td>
</tr>
<tr>
<td>Type of container used:</td>
<td></td>
</tr>
<tr>
<td>Total number of containers or lot size:</td>
<td></td>
</tr>
<tr>
<td>Number of doses per container:</td>
<td></td>
</tr>
<tr>
<td>Date of start of period of validity (e.g. manufacturing date):</td>
<td></td>
</tr>
<tr>
<td>Date of expiry (DD/MON/YYYY):</td>
<td></td>
</tr>
<tr>
<td>Storage conditions:*</td>
<td></td>
</tr>
<tr>
<td>* Some products may also have approved extended controlled temperature conditions at the end of use.</td>
<td></td>
</tr>
<tr>
<td>Diluent lot number(s) (if applicable):</td>
<td></td>
</tr>
<tr>
<td>Diluent expiry date(s) (if applicable):</td>
<td></td>
</tr>
<tr>
<td>Marketing authorization number (member state) issued by:</td>
<td></td>
</tr>
<tr>
<td>Name and address of manufacturer:</td>
<td></td>
</tr>
<tr>
<td>Site(s) of manufacturing:</td>
<td></td>
</tr>
<tr>
<td>Name and address of marketing authorization holder (if different ):</td>
<td></td>
</tr>
</tbody>
</table>

This batch has been examined using documented procedures which form part of a quality system which is in accordance with the ISO/IEC 17025 standard. The release decision is based on the elements described in paragraph 7.3 of the Lot release guideline.

This batch has been found compliant with the above by the institute below, member of the WHO Network of National Vaccine Control Laboratories.

Name (typed): . .......................................................... ..........................................................
Institute: .......................................................... ..........................................................
Position: .......................................................... ..........................................................
Signature: .......................................................... ..........................................................
Date: .......................................................... ..........................................................

1 Name of manufacturer.
2 If any national requirements have not been met, specify which one(s) and indicate why the release of the lot(s) has nevertheless been authorized by the NRA.
3 With the exception of provisions on distribution and shipping, which the NRA may not be in a position to assess.
4 The relevant WHO Technical Report Series, No. XXX, Annex Y.

* The relevant text from this guideline is shown in Box 1 on page 7
The Self-medication Collaborative Asian Regulator Expert Roundtable (Self-CARER)

The Self-medication Collaborative Asian Regulator Expert Roundtable (Self-CARER) is an international coalition of medicines regulatory authorities in the Asia Pacific region. It is a unique regulatory network in the sense that it deals with non-prescription medicines.

The Self-CARER members meet annually to devise coordinated and strategic plans to improve the effectiveness and efficiency of regulatory activities concerning self-care medicines in the region. Self-CARER is a non-binding forum devoted to fostering mutual public health and economic benefits in its member nations and regions through enhanced self-care medicine product regulation.

Background

The regulations applicable to pharmaceutical products in the Asia Pacific region, including over-the-counter (OTC) and traditional medicines, vary significantly between regulatory authorities. Currently, the majority of health and medical product regulators in this region focus their attention and resources primarily on issues related to prescription products rather than non-prescription medicines. In connection with the activities described in this article, the term “self-care medicines” is used instead of more specific terms such as “OTC” (Box 1).

Unlike prescription drugs, self-care medicines do not necessarily need to be used under the supervision and guidance of a medical professional. As such, considering the reasons for which a given medicine is designated as a self-care medicinal product, its review, registration, and post-approval regulation should be conducted within a framework that is optimized for this product category.(1) Success in this regard would increase the efficiency of self-care medicine product reviews and thus bring about needed improvements in public access to safe and efficacious non-prescription medicines throughout the Asia Pacific region.

To accomplish this goal, leaders of regulatory authorities in the region, with support from the corresponding industry association,(2) determined that greater international cooperation was necessary to identify mutually beneficial regulatory reforms, and that harmonization would then be integral to fully realizing the benefits of such reforms.

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The Self-CARER network
To promote regulatory cooperation and harmonization in the area of self-care medicines, the Self-medication Collaborative Asian Regulator Expert Roundtable (Self-CARER) was formed in 2014. Chaired by the Thai Food and Drug Administration, it is the first platform to materialize cooperative efforts and opinion exchange between Asia Pacific regulators focused on self-care medicine products. The members of Self-CARER meet annually to discuss initiatives and concerns related to improving self-care medicine regulation in the Asia Pacific region in a non-binding, mutually respectful environment.

Past efforts
To date, Self-CARER has focused its activities on three major areas with the goal of realizing overall improvements in self-care medicine product regulation: (1) streamlining product review and registration, (2) establishing a shared directory of active pharmaceutical ingredients (APIs) found in self-care medicines, and (3) simplifying the criteria governing the reclassification of prescription products to self-care medicine status.

Simplified registration
The safety and efficacy profiles of most APIs used in self-care medicines have been established through evidence generated over many years of appropriate use. In some regulatory environments the physicochemical, quality, purity, and potency attributes of self-care medicine APIs are standardized in the form of pharmacopoeias or drug monographs. This practice allows for more rapid and consistent review and classification of self-care medicine products in comparison to prescription products, which require full-scale reviews.

Despite the differences between prescription-only and self-care medicines, various regulatory authorities in the Asia Pacific region use the same procedure to review applications for new self-care medicine products and those for switching from prescription-only status. This suggests that there is room for improvement in the efficiency of product reviews by such regulators.

Box 1: What are “self-care medicines”?
In order to avoid misunderstanding over the meaning of over-the-counter (OTC) products, which can vary between regulatory authorities, the members of Self-CARER newly defined and adopted the term “self-care medicine” at the Self-CARER’s inaugural meeting. The new term refers to all OTC and off-the-shelf medicines usable by consumers to treat self-recognized minor injuries or illnesses. The members agreed to use this term in connection with all future Self-CARER activities and discussions.

In relation to this definition, WHO defines “self-medication” as “the selection and use of medicines by individuals to treat self-recognised illnesses or symptoms.”

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In relation to this definition, WHO defines “self-medication” as “the selection and use of medicines by individuals to treat self-recognised illnesses or symptoms.”
At previous Self-CARER meetings, the members discussed options for simplified product registration following two potential models: abbreviated registration or a monograph system. The Self-CARER members are currently in ongoing discussions with the goal of producing various ideas for ways to simplify or streamline product reviews and registration systems. These ideas will take the form of model operating procedures that will serve to aid regulators in converging on mutually agreed-upon best practices. Ideas proposed thus far have included reforms such as exempting certain types of data from application requirements for self-care medicines, allocating dedicated review staff to self-care products to simultaneously build expertise and increase efficiency, adopting a monograph system, or establishing a framework for receiving and utilizing reference data from pre-defined reference regulatory authorities.

**Ingredient directory**

In a departure from the status quo in which the different regulators each maintain their own databases, it has been proposed to establish a single database of APIs contained in self-care medicines. The primary advantages of such a shared repository include greater regulatory efficiency as well as mitigation of linguistic and cultural obstacles encountered through the use of the existing multiple parallel databases. However, although the members recognize the utility of a shared ingredient directory, various concerns remain such as how this initiative will be funded, what form of entity will be tasked with maintaining the database, and what types of content are most critical. Discussions between the members concerning potential solutions are currently ongoing.

**Reclassification criteria**

Another common issue recognized by the members of Self-CARER is that the criteria used to reclassify or “switch” prescription-only medications to self-care medicine or off-the-shelf status are an important area for discussion.

The most common factors considered by Asia Pacific regulators in such applications for reclassification include the safety profile of a medicine under its approved use, the severity and frequency of adverse drug reactions, the pharmacokinetic and pharmacodynamic properties of the APIs, product indication(s), route(s) of administration, extent of use, time on the market, and risks when the product is misused. Sharing of information regarding these criteria among the members of Self-CARER would both increase the speed of application reviews by each regulator as well as improve the consistency of the review results.

**Obstacles**

Self-CARER functions as a level field for discussions between the regulators of both developed and developing countries and regions on how to achieve greater effectiveness and efficiency in the regulation of self-care medicines. However, Self-CARER faces various challenges, such as:

- Lack of specific review/registration schemes for self-care medications, or of assigned dedicated review staff;
- Difficulty to achieve necessary legislation changes without disrupting routine operations;
- Scarce resources for necessary training of reviewers regarding evaluation processes and best practices for decision-making;
- Shortages of qualified review staff; and
- Lack of a shared model for how to simplify product review/registration procedures.
To overcome these obstacles, Self-CARER is currently considering working with each of its members as needed to develop basic model regulatory frameworks that are still similar enough to those of other Asia Pacific regulators to promote streamlining and harmonization across the region.

**Future goals**

In the years to come, Self-CARER plans to focus its efforts on overcoming its various challenges and bringing about both public health and economic benefits for its members. The network intends to prioritize policy adjustments that can increase regulatory efficiency by several means: creating a review scheme for self-care medicines that is separate from that used for prescription-only products, devising ways to further streamline review processes, and developing concrete plans to expand the safe and effective use of self-care medicines.

**References**


Norms and standards

70 years of WHO standards on medicines quality


The Expert Committee on Specifications for Pharmaceutical Preparations advises the WHO Director-General and Member States on matters of medicines quality assurance. When it started its work in 1947 it focused on maintaining The International Pharmacopoeia. Its scope of work broadened and deepened over the years, reflecting the emergence of new approaches to quality management in pharmaceutical production and regulation. This article highlights the Committee’s main areas of work. A list of current guidelines and work in progress is provided in the Appendix.

Background

Expert Committees advise the WHO Director-General and Member States in technical areas related to public health. Their members are recruited from WHO’s Expert Advisory Panels. Stringent procedures are in place for their selection and for the management of conflicts of interest. The technical guidance adopted by the Committees is developed through a public consultation process. Once adopted, the guidelines are published as annexes to the Committees’ meeting reports in the WHO Technical Report Series (TRS).

The Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) is one of the WHO Expert Committees that meet regularly. It advises the WHO Director-General and Member States on quality assurance during the life cycle of medicines and in their regulation. In 2017 it looks back on seventy years of standard-setting work.

History

The ECSPP was established as “Expert Committee on the Unification of Pharmacopoeias”. It met for the first time in 1947 (1), and the report of its fourth session was published in 1950 in the very first WHO Technical Report Series (2). At that time many of today’s WHO Member States were not yet part of WHO. Modern concepts of medicines quality assurance were only starting to emerge, often in response to unfortunate incidents with medicines that caused serious harm (Box 1).

The decades that followed saw the development of scientific approaches to ensure the quality, safety and efficacy of pharmaceutical products. However, many developing countries did not have the

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1 See www.who.int/about/collaborations/expert Panels/en/. Others are the WHO Expert Committee on Biological Standardization (ECBS), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the WHO Expert Committee on Selection and Use of Essential Medicines and the WHO Expert Committee on Drug Dependence.
resources to establish medicines regulatory authorities that could effectively protect the health of their populations.

The operations of the pharmaceutical industry are guided by the legal requirements in force in the target markets. In a globalized marketplace this often means that high quality medicines are being produced for use in stringently regulated environments, while fewer requirements and lower standards are applied for medicines used elsewhere. Moreover, as starting materials and services are sourced from across the globe, local weaknesses in

**Box 1: Medicines quality assurance: a timeline**

- **1937** Over 100 people in the U.S. die following the use of an elixir which used diethylene glycol as a solvent without any safety testing
- **1937** League of Nations sets up a Technical Commission of Pharmacopoeial Experts
- **1938** U.S. Federal Food, Drug and Cosmetic Act introduced, with a premarket notification requirement for new drugs
- **1947** WHO Interim Commission takes over the work on pharmacopoeias from the League of Nations and reports on its first session
- **1948** First World Health Assembly establishes the “Expert Committee on the Unification of Pharmacopoeias” (renamed twice thereafter)
- **1956–60** Thalidomide marketed in 46 countries worldwide, leading to an estimated 10 000 babies being born with deformities
- **1962** New U.S. legislation requires proof of safety and efficacy before approval of new drug applications for the first time. FDA authorized to require compliance with current Good Manufacturing Practices (GMP)
- **1963** World Health Assembly adopts Resolution WHA16.36 on Clinical and pharmacological Evaluation of Drugs. U.K. Committee of Drug Safety established
- **1969** First WHO guidance on *Good practices in the manufacture and quality control of drugs* published with World Health Assembly Resolution WHA22.50, (following up on Resolutions WHA20.34 of 1967 and WHA21.37 of 1968)
- **1970** Pharmaceutical Inspection Convention (now: Pharmaceutical Inspection Cooperation Scheme, PIC/S) established, with GMP guidelines based on those of WHO
- **1975** Multistate procedure for medicines registration introduced in Europe, starting harmonization of medicines regulation
- **1984** U.S. legislation introduces bioequivalence studies for generic medicines in lieu of clinical efficacy and safety studies
- **1985** First international conference on essential medicines policies held in Nairobi, leading to the adoption of the WHO revised drug strategy
- **1989** At the Fifth International Conference of Drug Regulatory Authorities (ICDRA) Europe, Japan and U.S agree on action plans for harmonization. Pharmacopoeial Discussion Group formed
- **1990** International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) established
- **1990** First WHO *Guiding principles for small national drug regulatory authorities* published
- **2001** UN Secretary General Kofi Annan calls for a Global Fund to fight HIV, tuberculosis and other infectious diseases
- **2001** WHO prequalification of medicines launched to assess key medicines against WHO norms and standards
- **2005** WHO guideline on assessing bioequivalence of fixed-dose combinations published, supporting a global scale-up of antiretrovirals
- **2006** WHO *Model Quality Assurance System for procurement agencies* published, required for all Global Fund-financed health products
- **2008** WHO biowaiver procedure proposed
- **2010** WHO introduces joint assessments with East African Community and joint inspections
- **2014** World Health Assembly Resolution WHA67.20 makes the first-ever global-level call for Regulatory capacity-building
- **2015** EMA suspends over 700 products over concerns with their bioequivalence data
- **2016** WHO guideline on *Good data and record management practices* published
regulatory control can have global impact. Today all the world's regulatory authorities – including the well-established ones – are calling for cooperation and convergence of standards to close the regulatory gaps.

These developments have been shaping the need for comprehensive WHO guidance on medicines quality assurance that can be implemented in all Member States.

**WHO technical guidance**

In the 70 years of its history the ECSPP has broadened its scope of work to cater for the changing needs. It has come to provide unified international norms and standards for all aspects of quality assurance in a medicine's life cycle, supporting the global move towards convergence, collaboration and reliance among regulatory authorities. The current guidelines are listed in **Appendix 1**. An overview of the ECSPP's work in the different areas is provided below.

**Pharmacopoeial standards**

Maintaining pharmacopoeial standards was the initial mandate of ECSPP. The first volume of *The International Pharmacopoeia* was published in 1951. The current Sixth Edition includes monographs for 439 pharmaceutical substances, 142 dosage forms and 27 radiopharmaceuticals, 174 infrared reference spectra, as well as monographs on general dosage forms, analytical methods and other supplementary texts. By providing publicly available standards for testing of commonly used medicines, many which are not included in any other pharmacopoeia, *The International Pharmacopoeia* fulfils a unique public health role.

Although “unification of pharmacopoeias” has been a goal since the Committee took up its work, the world's pharmacopoeias have evolved separately. The WHO Index of World Pharmacopoeias\(^1\) lists pharmacopoeial authorities of 53 countries and two regions.

In 2012, WHO convened representatives of pharmacopoeias from 23 countries for the first time to discuss options for convergence of standards. The WHO international meetings of world pharmacopoeias became a regular event and have served as a forum to develop a guideline on Good Pharmacopoeial Practices (GPhP), published in 2016. By promoting collaboration among pharmacopoeias this

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guidance is expected to lead to a prospective harmonization of standards, with significant potential benefits for manufacturers and regulatory authorities.

**Quality control**

In the early days of the ECSPP’s history quality control testing was the mainstay of medicines control. While the emphasis has shifted away from pre-market testing towards an ongoing control whether batches supplied meet the agreed specifications, quality control testing remains an important regulatory function. At a time when shortages of various types of medicines are a persistent concern, efficient quality monitoring is critical for continued supply of products.

WHO provides detailed guidance on all aspects of laboratory testing. In 1984 the Committee recommended that countries should set up national pharmaceutical quality control laboratories, and provided guidance on organization and staffing. The first text on good laboratory practice (GLP) followed in 1987 – last revised in 2010 – and a specific text for pharmaceutical microbiology laboratories was added in 2011. WHO prequalification of quality control laboratories was introduced in 2006 and is based on the standards adopted by the ECSPP.

**Production and inspections**

When modern medicines regulation started to develop in the 1960s it was recognized that quality cannot be “tested into a product”. Instead it must be built into a product at every step of development and production. The regulatory paradigm has shifted from quality control of the finished product to control of the manufacturing processes, as verified in inspections.

Accordingly, the ECSPP took on the development of norms and standards for the manufacture of finished pharmaceutical products and their active pharmaceutical ingredients (APIs). The first WHO guideline on good manufacturing practice (GMP) was published in 1969 (3) and formed the basis for the GMP text of the Pharmaceutical Inspection Convention (PIC) upon its establishment in 1970.

The WHO GMP guidance has been continuously updated and supplemented by guidance on specific aspects and for specific product types. The current texts reflect today’s focus on quality management systems with effective mechanisms to identify, quantify and manage risks throughout the entire life cycle of a medicine.

Guidance on GMP inspections and classification of deficiencies has also been updated to support collaboration and reliance, reducing the burden of inspections on both manufacturers and regulators. A text on desk reviews of inspection information is in preparation.

**Distribution**

As pharmaceutical operations have become globalized, active ingredients and finished products cross many borders before they reach the end users. Joint global efforts are needed to safeguard the quality of pharmaceuticals in the supply chains. WHO has provided guidelines on good practices for trade and distribution both for medicines and starting materials as well as good storage practices including for time-and temperature-sensitive products.

Procurement agencies play a crucial role in assuring the quality of medicines that they delivered. The WHO *Model Quality Assurance System for procurement agencies* (MQAS) was first adopted in 2006. It provides a comprehensive toolkit for procurement organizations to safeguard the quality of medicines at all stages, from the qualification of suppliers throughout purchasing, storage
and distribution of the products. The MQAS was updated in 2014 with input from the major international organizations that procure and/or fund medicines.

Quality surveys through testing of samples provide information about the quality of medicines circulating on the market at a given time. They are useful to verify the effectiveness of other regulatory measures such as marketing authorization, inspections and post-marketing surveillance activities. The 2016 Guidelines on the conduct of surveys of the quality of medicines outline the steps to consider when preparing and conducting a sample testing survey.

Special methods are required to detect and test products that have been introduced into the supply chains with fraudulent intent. Responding to a need expressed by quality control laboratories in a survey, WHO proposes a new guidance on testing of suspected spurious, falsely-labelled, falsified and counterfeit medicines. This technical guidance complements the work of the Member State Mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products, which was established in 2012.3

Good pharmacy practice
Pharmacists play an important role in delivering medicines to patients. WHO and the International Pharmaceutical Federation (FIP) have a long history of collaboration in providing guidelines on good pharmacy practice. The most recent addition is a “points to consider” document on preparing children-specific medicines that are not available as authorized products.

3 WHO Essential medicines and health products. WHO Member State Mechanism. www.who.int/medicines/regulation/ssffc/mechanism/en/

Regulation and prequalification
Work on the first WHO Guidelines for small drug regulatory authorities started in 1985 as a component of the Organization’s Revised Drug Strategy (4). The regulatory guidance adopted by the ECSPP has been completed and updated in line with evolving regulatory concepts. Unlike national and regional regulations, the WHO guidelines reflect global perspectives on issues such as stability of medicines across climatic zones, or the selection of comparator products when demonstrating bioequivalence of generics.

Comprehensive guidance has been generated by the Committee to underpin WHO prequalification of medicines. Established in 2001, when HIV treatment was unaffordable in the public sector of most WHO Member States, this programme has increased global access to affordable key medicines of assured quality. The WHO guidance on assessing bioequivalence of fixed-dose combinations, which was published in 2005, contributed significantly to scaling up global access to ARV therapy (5). Prequalification was subsequently extended to additional medicines categories. A procedure to prequalify APIs in their own right was introduced in 2009. Since 2013 WHO offers a collaborative registration procedure for WHO-prequalified medicines in participating countries, which accelerates the review process while ensuring that the stringent quality standards used in prequalification are maintained.

The WHO prequalification team provides important input to the ECSPP’s work from its experience with implementing stringent standards in a wide variety of settings. Several prequalification guidelines have been subsequently adapted for use by regulatory authorities.

With increasing globalization, digitalization and outsourcing of services,
new issues are emerging. An example are the recurring concerns about data integrity at contract research organizations that perform bioequivalence studies. The 2016 WHO *Guideline on good data and record management practices* is the first text of its kind globally to bring together the relevant information in one place, completing the existing good practice guidelines in the various areas (GXP).

Today, no regulatory authority can achieve its mandate without using smart ways of reviewing data and making decisions. 2015 saw the publication of the *WHO guidelines on Good review practices* intended to support Member States, including those with less mature regulatory systems. A more comprehensive, high level framework document on all aspects of *Good regulatory practices* is under development.

Reliance on the decisions of stringent regulatory authorities (SRA), defined as members or associates of ICH, is provided for in several WHO guidelines. As ICH is evolving to become a global organization, this definition need revisiting. At its 51st Meeting the ECSPP adopted an interim revised definition and noted the work being done towards new assessment approaches that will enable collaboration and reliance on regulatory authorities with proven efficiency in specific fields.

Regulatory capacity needs to be strengthened in additional areas, notably for medical devices, including diagnostics. This complex and growing product group is increasingly important for public health, yet few Member States regulate it fully. The 2016 WHO global model regulatory framework for medical devices comes at a time when there is significant scope for the introduction of unified standards in this area.

## Conclusion

WHO is the only organization with a mandate to protect global health. The development, establishment and promotion of international standards for pharmaceuticals are among the functions laid down in its constitution. Its technical guidance on medicines quality is designed to serve regulatory authorities of all Member States, as well United Nations agencies and other major international bodies. It provides a technical platform for convergence as recommended by the 17th International Conference of Drug Regulatory Authorities (ICDRA) (6). At a time when access to essential medicines is a pressing issue on the sustainable development agenda, the ECSPP’s standard-setting work makes a unique and critical contribution towards more equitable access to needed medicines of assured quality.

## References


**Appendix 1: WHO guidelines on medicines quality assurance**

Only the latest revised versions of the guidelines are listed.

The guidelines shown under each heading are listed in chronological order of their adoption. The texts are available in the different sections of the WHO medicines “Guidelines” website ([www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/)).

Texts marked with an asterisk (*) are under revision or under development. The draft texts or revisions are available in the public consultation section of the above website, titled “Current Projects”, at [www.who.int/entity/medicines/areas/quality_safety/quality_assurance/projects/](http://www.who.int/entity/medicines/areas/quality_safety/quality_assurance/projects/).

### Quality control

#### Pharmacopoeial standards and practices

- **The International Pharmacopoeia, Sixth Edition** (1) 2016

  - Recommendations on Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products
    - TRS 908 Annex 1 2003
  
  - The International Pharmacopoeia – related substances tests: dosage form monographs guidance notes
    - TRS 943 Annex 1 2007

  - General guidelines for the establishment, maintenance and distribution of chemical reference substances
    - TRS 943 Annex 3 “

  - List of available International Chemical Reference Substances and International Infrared Reference Spectra
    - TRS 953 Annex 1 2009

  - List of reference substances of other pharmacopoeias found to be suitable for use according to The International Pharmacopoeia
    - Living document (2)

  - Release procedure of International Chemical Reference Substances
    - TRS 981 Annex 1 2013

  - Procedure of the development of monographs and other texts for The International Pharmacopoeia
    - TRS 992 Annex 1 2015

  - Trade names of stationary phases found suitable in performing chromatographic tests described in The International Pharmacopoeia
    - Living document (3)

  - Updating mechanism for the section on radiopharmaceuticals in The International Pharmacopoeia
    - TRS 992 Annex 2 2015

  - Good pharmacopoeial practices
    - TRS 996 Annex 1 2016

  - *Glossary

  - *The International Pharmacopoeia: revised concepts and future perspectives (Update of TRS 908, Annex 2)
    - To be published 2017

#### Quality control testing

- *Considerations for requesting analyses of drug samples
  - TRS 902 Annex 4 2002

- *Model certificate of analysis
  - TRS 902 Annex 10 “

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70 years of WHO standards on medicines quality

**Quality control laboratories**

WHO good practices for pharmaceutical quality control laboratories

- Appendix 1: Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

WHO good practices for pharmaceutical microbiology laboratories

WHO guidelines for preparing a laboratory information file

*Prequalification of quality control laboratories, see under “WHO Prequalification”*

**Development**

Pharmaceutical development of multisource (generic) finished pharmaceutical products – points to consider

Development of paediatric medicines: points to consider in formulation

**Production**

**Good manufacturing practices (GMP)**

*General guidelines*

WHO GMP for pharmaceutical products: main principles

*Supplementary guidelines*

Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans

GMP: authorized person - role, functions and training

Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients

Guidelines on Good Manufacturing Practices for radiopharmaceutical products

Supplementary guidelines on good manufacturing practices for the manufacture of herbal medicines

*Guidelines on validation (includes 7 appendices)*

- Appendix 4: Analytical method validation
- Appendix 5: Validation of computerized systems
- Appendix 6: Qualification of systems and equipment
- Appendix 7: Non-sterile process validation

WHO good manufacturing practices for active pharmaceutical ingredients

WHO good manufacturing practices for pharmaceutical products containing hazardous substances

WHO good manufacturing practices for blood establishments

*WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms*

*WHO good manufacturing practices for sterile pharmaceutical products*

Water for pharmaceutical use

Good Manufacturing Practices (GMP) for biological products (4)
### Technology transfer

- **WHO guidelines on transfer of technology in pharmaceutical manufacturing**
  - TRS 961 Annex 7 2011

### Inspections

- *Provisional guidelines on the inspection of pharmaceutical manufacturers*  
  - TRS 823 Annex 2 1992
- *Inspection of drug distribution channels*  
  - TRS 885 Annex 6 1999
- *Quality system requirements for national GMP inspectorates*  
  - TRS 902 Annex 8 2002
- *Guidelines on pre-approval inspections*  
  - TRS 902 Annex 7 2011
- **WHO guidelines for drafting a site master file**  
  - TRS 961 Annex 14 2011
- **General guidance on “hold-time” studies**  
  - TRS 992 Annex 4 2015
- **Guidance on GMP: Inspection Report**  
  - (includes Model certificate of GMP in Appendix 1)
    - TRS 996 Annex 4 2016

### Distribution

- **Proposed guidelines for implementation of the WHO certification scheme**  
  - TRS 823 Annex 3 1992
- *Guidelines on import procedures for pharmaceutical products*  
  - TRS 863 Annex 12 1996
- **WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation**  
  - TRS 917 Annex 3 2003
- **WHO good distribution practices for pharmaceutical products**  
  - TRS 957 Annex 5 2010
- **WHO Certification scheme on the quality of pharmaceutical products moving in international commerce: Questions and Answers (Q & A)**  
  - WHO Drug Information 30 (3) 2016
- **Good trade and distribution practices for starting materials**  
  - TRS 996 Annex 6 2016

### Procurement

- **Procedure for assessing the acceptability, in principle, of procurement agencies for use by United Nations agencies**  
  - TRS 917 Annex 6 2003
- **Guidelines for the preparation of a procurement agency information file**  
  - TRS 917 Annex 7
- **Model quality assurance system for procurement agencies**  
  - TRS 986 Annex 3 2014
    - (Includes Appendix 6: Interagency finished pharmaceutical product questionnaire based on the model quality assurance system for procurement agencies)
- **Assessment tool based on the model quality assurance system for procurement agencies: aide-memoire for inspection**  
  - TRS 986 Annex 4 2014
- **A harmonized self-assessment tool for procurement agencies**  
  - WHO Drug Information 28 (4) 2014

### Storage

- **Guide to good storage practices for pharmaceuticals**  
  - TRS 908 Annex 9 2003
- **Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products**  
  - TRS 961 Annex 9 2011

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(4) Also adopted by the Expert Committee for Biological Standardization (ECBS)

(5) The TRS annex includes the introductory sections and an overview of the 15 technical supplements. The latter are available online at [www.who.int/medicines/areas/quality_safety/quality_assurance/distribution/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/distribution/en/)
Continued

Technical supplement materials to the WHO guidance for storage and transport of time- and temperature-sensitive pharmaceutical products

TRS 992 Annex 5 (5) 2015

Monitoring medicines quality

Guidelines on the conduct of surveys of the quality of medicines

TRS 996 Annex 7 2016

“WHO guidance on testing of “suspect” substandard/spurious/falsely-labelled/falsified/counterfeit medicines

In preparation

Good pharmacy practice (6)

Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services

TRS 961 Annex 8 2011

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

TRS 996 Annex 2 2016

WHO prequalification (6)

Medicines (7)

Guidelines on the requalification of prequalified dossiers

TRS 957 Annex 6 2010

Procedure for prequalification of pharmaceutical products

TRS 961 Annex 10 2011

Guidelines on submission of documentation for a multisource (generic) finished product: general format: preparation of product dossiers in common technical document format

TRS 961 Annex 15

Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part

TRS 970 Annex 4 2012

Guidance on variations to a prequalified product

TRS 981 Annex 3 2013

Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities

TRS 986 Annex 5 2014

Collaborative procedure between the World Health Organization (WHO) prequalification team medicines and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines

TRS 996 Annex 8 2016

Active pharmaceutical ingredients

Guidelines on active pharmaceutical ingredient master file procedure

TRS 948 Annex 4 2008

Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products

TRS 953 Annex 4 2009

Other related products

Procedure for Assessing the acceptability, in principle of male latex condoms for purchase by United Nations agencies

TRS 948 Annex 2 2008

Procedure for Assessing the acceptability, in principle of TCU 380A intrauterine devices for purchase by United Nations agencies

TRS 948 Annex 3 “


(7) Prequalification of vaccines is conducted in line with standards provided by the WHO Expert Committee for Biological Standardization; prequalification of diagnostics is largely based on standards proposed by the International Medical Device Regulators Forum (IMDRF).
### Quality control laboratories

*Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies (Update of TRS 962, Annex 12)*

To be published 2017

### Regulatory guidelines

#### General

WHO Guideline on quality risk management

TRS 981 Annex 2 2013

#### Contract research, data management

- Guidelines for the preparation of a contract research organization master file
  
  TRS 957 Annex 7 2010

- Guidance on good data and record management practices
  
  TRS 996 Annex 5 2016

#### Interchangeability of comparator and generic products

- Multisource (generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability *(8)*
  
  TRS 992 Annex 7 2015

- Guidance for organizations performing in vivo bioequivalence studies
  
  TRS 996 Annex 9 2016

- *Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics classification system*
  
  To be published 2017

- *General Background notes on the list of international comparator pharmaceutical products (Update of TRS 992, Annex 8)*
  
  To be published

- *International Comparator Products List for equivalence assessment of interchangeable multisource (generic) products*
  
  Living document

#### Stability

- *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products*
  
  TRS 953 Annex 2 2009

- Stability conditions for WHO Member States by Region (Table 2 of TRS 953 Annex 2)
  
  Living document *(9)* 2015

#### Other

- *Guidelines on packaging for pharmaceutical products*
  
  TRS 902 Annex 9 2002

- *Guidelines for registration of fixed-dose combination medicinal products*
  
  TRS 929 Annex 5 2005

- WHO guidelines for sampling of pharmaceutical products and related materials
  
  TRS 929 Annex 4 2005

- Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part
  
  TRS 986 Annex 6 2014

*(8) Includes information on WHO's current policy regarding biowaivers. The table with classifications according to the Biopharmaceutics Classification System (BCS) in the 2006 *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms* (TRS 937, Annex 8) is under revision and will be made available as a living document. The 2006 biowaiver guidance remains on the website as it includes some useful information, e.g. in Sections 1.4 and 1.6 on the rationale for the setting of criteria.*

### Norms and standards

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<td>*WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines</td>
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#### Medical devices

| *WHO global model regulatory framework for medical devices including IVD medical devices | To be published | 2017 |

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(10) See https://extranet.who.int/prequal/content/faster-registration-fpps-approved-sras
(11) Available at: http://apps.who.int/medicinedocs/en/d/Js5516e/
Vaccine control

Feasibility of a serological potency assay for rabies vaccines for human use

The method currently recommended to determine the potency of rabies vaccines, the NIH mouse protection test, is demanding to perform and causes significant suffering to experimental animals. WHO initiated a feasibility study in order to determine whether a simpler serological assay developed at the Paul-Ehrlich-Institut (PEI) may be a suitable alternative for use by vaccine control laboratories globally. The findings suggest that the serological assay is promising but needs further verification.

Introduction

The National Institute of Health (NIH) potency test, which is based on a mouse protection assay, is used to determine the potency of rabies vaccines. (1) However, only a limited number of national control laboratories are performing this assay due to its high requirements in terms of safety and technical capability. Moreover, this assay requires high animal numbers and causes severe suffering to the test animals. It is also known to have high variability and can be problematic in terms of meeting all of the validity criteria. (2)

In the interest of refining, reducing and replacing animal testing (3R principle) the Paul-Ehrlich-Institut (PEI) has developed an alternative method (3, 4) that could potentially replace the rabies mouse challenge test. The proposed method is a multi-dose serological assay, based on vaccination of mice and subsequent determination of neutralizing antibodies in vitro.

The WHO Technical Assistance and Laboratory Services (TAL) Group initiated and coordinated a small scale feasibility study to evaluate whether this alternative assay can be successfully used for the potency determination of rabies vaccines for human use, and whether the test protocol can be transferred and applied at other laboratories.
Method

The study was performed at PEI and at the Institute of Biological Products (IBP) in Thailand. Training was provided to ensure the appropriate and timely performance of the testing.

Each of the two participating laboratories was asked to test a panel of three prequalified rabies vaccine samples against a standard vaccine (the WHO 6th International Standard for rabies vaccine), using the serological assay. One of the three test vaccines was heat-treated in order to induce a sub-potent quality. This sub-potent vaccine was tested using both serology and the NIH mouse protection test.

Each test vaccine was investigated in two independent test runs at four dilutions, against four equivalent dilutions of the standard vaccine. A fifth dilution of the standard vaccine equivalent to the minimum required potency (2.5 IU/ml) was added to investigate the suitability of a single-dose approach (cut-off test).

Groups of mice were immunized twice with either the test vaccine or the standard vaccine. Each dilution of each vaccine was administered into 10 mice.

Seven days after the second immunization blood samples were taken and the sera were tested for rabies antibodies using the proposed virus neutralization assay, a modified rapid fluorescent focus inhibition test (RFFIT).

The statistical analysis was performed at PEI and by Dr Stanley Norris Deming, Statistical Designs, Houston. Individual titers as well as pool sera were evaluated with a parallel line model to obtain a potency value for each sample relative to the WHO standard vaccine (with an assigned potency of 8 IU/ml).

Findings – in brief

While differences with regard to estimated potencies were observed between the participating laboratories, a vaccine dose-dependent immune response of rabies antibody titres could be shown in almost all of the tests. The results of the NIH tests (manufacturer’s results at time point of release) could only partly be confirmed by the serological assay. This comes as little surprise since the comparison is based on the measurement of two different parameters: survival rates are enumerated with the NIH test, whereas antibody responses are determined in the serological assay.

Development of a single dilution assay (cut-off test) did not seem feasible as the serum activities obtained with the standard, adjusted to the minimum potency, were higher than those obtained with the test vaccines in all tests.

When potencies were calculated for individual sera, 3 out of 12 tests gave estimated curves that fulfilled the validity criteria for both linearity and parallelism. When potencies were calculated for serum pools, parallelism was observed in all cases, provided that deviations from linearity were accepted.

The sub-potent vaccine was correctly classified by means of the NIH test at both laboratories. In the serological assay, when analyzing serum pools, the sub-potent quality of the vaccines was correctly assigned in 3 out of 4 cases.

Conclusions

Routine testing of individual sera using the serological assay does not seem appropriate due to the high number of plates to be handled and the difficulty to meet the current validity criteria. Testing of serum pools seems preferable. This
was a first feasibility study. The suitability of the serological assay for the potency quantification of rabies vaccines for human use would need to be further proven. A further, exhaustive publication on the study is in preparation.

References
Safety news

Safety warnings

Belladonna-containing teething products: risk to children
United States of America – An FDA laboratory analysis has found inconsistent amounts of belladonna in certain homoeopathic teething tablets, sometimes far exceeding the amount claimed on the label. The agency is warning that homoeopathic teething tablets containing the toxic substance belladonna pose a risk to infants and children, who may experience seizures, difficulty breathing, lethargy, excessive sleepiness, muscle weakness, skin flushing, constipation, difficulty urinating and agitation. The FDA urges consumers not to use these products. Homoeopathic teething products have not been evaluated or approved by the FDA for safety or effectiveness. In 2016 the FDA had warned consumers against the use of such products after receiving adverse event reports. (1)

Australia – Urgent testing conducted by the TGA in response to the safety concerns described above did not identify any quality issues. (2)

(2) TGA Update, 1 February 2017.

Hyoscine butylbromide injection: serious adverse events in patients with underlying heart disease
United Kingdom – The MHRA has warned health professionals that hyoscine butylbromide (also known as butylscopolamine) injection (Buscopan*) can cause serious adverse effects, including tachycardia, hypotension and anaphylaxis. These effects can result in fatal outcomes, especially in patients with underlying cardiac conditions such as such as heart failure, coronary heart disease, cardiac arrhythmia or hypertension.

Injectable hyoscine butylbromide is used to treat acute muscular spasm and to reduce spasm in certain diagnostic procedures. The MHRA recommends to use this medicine with caution in patients that have any of the above-mentioned conditions. These patients should be monitored, and it should be ensured that resuscitation equipment as well as personnel who are trained in its use are readily available. The MHRA has reminded health professionals that hyoscine butylbromide injection remains contraindicated in patients with tachycardia.

The warning was published following nine reported deaths of patients in the United Kingdom after administration of hyoscine butylbromide injection. The product information has been updated to include the new recommendations.


Lenalidomide: reactivation of hepatitis B virus
Japan – The PMDA has informed health professionals that cases of reactivation of hepatitis B virus (HBV) have been reported in patients treated with lenalidomide (Revlimide*) in Japan. HBV reactivation may occur in HBV carriers or in patients with a history of HBV infection.
Recommendations have been added to the product information to test patients for HBV before starting treatment, and to monitor them during treatment with lenalidomide by appropriate measures such as periodic hepatic function tests and monitoring of HBV markers.

► PMDA Summary of investigation results and MHLW Revisions of precautions, 10 January 2017.

### Canagliflozin and other SLGT2 inhibitors: risk of amputations

**European Union** – The EMA has informed the public about a potential increased risk of lower limb amputations (mostly affecting the toes) in patients taking the sodium-glucose co-transporter 2 (SGLT2) inhibitors canagliflozin, dapagliflozin and empagliflozin. A review of these medicines was carried out by EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) in response to an increase in lower limb amputations observed in two ongoing clinical trials in patients treated with the canagliflozin. The mechanism by which canagliflozin may increase the risk of amputation is still unclear. An increased risk may also be associated with dapagliflozin and empagliflozin. Further data are expected from ongoing studies with these three SGLT2 inhibitors.

The product information for canagliflozin, dapagliflozin and empagliflozin will be updated based on available data; a warning of the potential increased risk of toe amputation highlighting the importance of routine preventative foot care will be included. For canagliflozin the risk of lower limb amputation will be listed as an uncommon side effect. If patients on canagliflozin develop significant foot complications such as infection or skin ulcers, treatment discontinuation should be considered.


### Gadolinium-based contrast agents: accumulation in the brain

**Canada** – Health Canada has conducted a safety review of gadolinium-based contrast agents (GBCAs) due to growing scientific evidence that gadolinium may accumulate in the brain following multiple contrast-enhanced magnetic resonance imaging (MRI) scans. The evidence suggests that gadolinium accumulation in the brain is higher with the use of linear agents than with the use of macrocyclic agents.

Although no health consequences have been identified with gadolinium accumulation in the brain, Health Canada is requiring updates to the product information for GBCAs, advising health professionals to limit the use of these contrast agents to situations where they are considered necessary, to use the lowest effective dose, and to assess the benefits and potential risks to individual patients before administering repeated doses. (1)

Reviews are also ongoing in the United States (2) and the European Union (3).


(2) FDA Drug safety announcement, 27 July 2015.

(3) EMA. Article 31 Review started, 18 March 2016.

### Restrictions

**Dienogest and ethinylestradiol: can be used for acne as a last resort**

**European Union** – The EMA has recommended that combination products containing dienogest and ethinylestradiol...
can be used for the treatment of moderate acne, but only if suitable local therapies or oral antibiotic treatment have failed, and only in women who also choose to use oral contraception.

Like all combined hormonal contraceptives dienogest and ethinyl-estradiol is associated with a risk of venous thromboembolism. While the risk is generally considered as low, available data are insufficient to quantify it for this specific combination. EMA recommends to consider each individual woman’s risk factors for venous thromboembolism before prescribing dienogest and ethinylestradiol for acne, and to reassess the need for continued treatment 3–6 months after starting treatment and periodically thereafter.


Fluoroquinolones: severe, disabling side effects

Canada – Healthcare professionals have been reminded about the potential for disabling and persistent serious adverse events with oral and injectable fluoroquinolone antibiotics. Health Canada is working with manufacturers to strengthen the prescribing information for these medicines.

The reminder follows rare reports of adverse events, including tendinopathy, peripheral neuropathy and central nervous system disorders, following systemic use of fluoroquinolones in Canada. In 2016, the U.S. FDA had restricted the use of fluoroquinolones to certain serious infections because of this risk. The EMA has started a review of this known risk associated with quinolones and fluoroquinolones (see under “Reviews started”).


Interferon beta-1b: thrombotic damage in small blood vessels

Japan – The PMDA has informed health professionals about reports of thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS) in patients treated with interferon beta-1b in Japan and in other countries. Patients should be monitored through periodic blood tests such as platelet tests or red blood cell counts, and/or renal function tests as appropriate. The product information has been updated accordingly. (1)

A warning about thrombotic microangiopathy (TMA), manifesting as TPP or HUS, was added to the EMA-approved product information for interferon beta-1b products in July 2014, together with recommendations for monitoring of
early symptoms, prompt treatment and discontinuation of interferon beta as soon as the reaction is diagnosed.\(^{(2)}\) The FDA-approved product information for interferon beta-1B was updated in December 2015 to include a warning about TMA.\(^{(3)}\)

► (1) PMDA Summary of investigation results and MHLW Revisions of precautions, 10 January 2017.

(2) EMA. Summary of product characteristics. Betaferon.

(3) FDA. Prescribing information for Extavia. May 2016.

**Menthol-containing topical analgesics: serious skin burns**

Canada – A Health Canada review has found a risk of serious skin burns with the use of certain OTC topical pain relievers containing menthol. Available data were not sufficient to determine whether the risk is linked to any specific brand, formulation or menthol concentration, or any ingredient other than menthol. The review also looked at the ingredients methyl salicylate and capsaicin, and did not find sufficient evidence to confirm the same risk with either of these ingredients alone.

A warning about the risk of burns is already included in the product information for certain products. Health Canada will publish an updated labelling standard for all menthol-containing topical analgesics.


**Tramadol: risk of serious breathing problems**

Canada – Based on the findings of a Health Canada safety review, the product information for tramadol-containing products has been updated to further highlight the risk of serious breathing problems. A warning has also been added that this risk is increased in patients who are “ultra-rapid metabolizers” of tramadol. The opioid medicine tramadol is approved in Canada to treat moderate to moderately severe pain in adults. Health professionals have been reminded that tramadol is not approved in Canada for use in patients under 18 years of age.\(^{(1)}\)

A similar review was initiated in the United States in 2015.\(^{(2)}\)


(2) FDA Drug safety communication, 21 September 2015.

**Varenicline and bupropion: risks said to be lower than expected**

United States of America – Based on the findings of a large clinical trial the FDA has determined that the benefits of varenicline and bupropion in helping people to stop smoking outweigh their risks of serious adverse effects on mood, behaviour or thinking. The results showed that these risks were present, especially in people having being treated for mental illnesses, but that in most patients they did not have serious consequences such as hospitalization. The warning sections of the medicines are being updated accordingly. Products containing bupropion, which is an antidepressant, will continue to carry a “Boxed Warning” about suicidality in patients treated with antidepressant medicines.

► FDA Drug safety communication, 16 December 2016.
**Herbal products**

**Toxic alkaloids in plant-based products**

Switzerland – Swissmedic has required marketing authorization holders to conduct risk evaluation and assays in order to mitigate the risk of toxic pyrrolizidine alkaloids contained in plant-based foods, teas and medicinal products. The toxic substances enter the products through weeds that are harvested with the plants.

Hundreds of structurally different pyrrolizidine alkaloids occurring in several thousand different plant species have been identified, and their toxic effect has been known for a long time. Many plant-based foods and medicinal plants are affected by the weed problem. It has been shown that measures going beyond the existing Good Agricultural and Collection Practice (GACP) are needed to ensure the quality and safety of these products. In May 2016 the EMA had published a statement with

**Reviews started**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Use</th>
<th>Concerns</th>
<th>Reviewing authority reference</th>
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</thead>
<tbody>
<tr>
<td><strong>Certain anaesthetics and sedatives</strong> when used in children under the age of three or in pregnant women during their third trimester</td>
<td>General anaesthesia and sedation</td>
<td>Lengthy use in young children or pregnant women may have potential negative effects on the development of children's brains</td>
<td>Health Canada Advisory, 22 December 2016. See also: FDA Drug safety communication, 14 December 2016</td>
</tr>
<tr>
<td><strong>Selexipag (Uptravi®)</strong></td>
<td>Treatment of pulmonary arterial hypertension</td>
<td>Deaths of 5 patients taking the medicine in France. Based on a preliminary review of available data, EMA advised that the product may continue to be used both in existing and new patients, provided that the recommendations and precautions in the current prescribing information are followed carefully.</td>
<td>EMA Press release, 10 February 2017. (As updated on 14 February 2017).</td>
</tr>
<tr>
<td><strong>Systemic and inhaled quinolones and fluoroquinolones</strong></td>
<td>Treatment of infections</td>
<td>Persistent serious side effects mainly affecting muscles, joints and the nervous system.</td>
<td>EMA, Article 31 Referral. Quinolone- and fluoroquinolone-containing medicinal products, 10 February 2017.</td>
</tr>
</tbody>
</table>
recommendations for risk management and quality control.

► **Swissmedic announcement, 6 February 2017.**

EMD. Public statement on contamination of herbal medicinal products/traditional herbal medicinal products with pyrrolizidine alkaloids; Transitional recommendations for risk management and quality control. 31 May 2016.

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### Non-compliance with good practices

**Micro Therapeutic Research Labs Pvt Ltd, India**

**European Union** – The EMA has started a review of medicines for which studies have been conducted by Micro Therapeutic Research Labs at its Chennai site or its Coimbatore site in India. This follows a good clinical practice (GCP) inspection in February 2016, which raised concerns about the study data used to support a number of marketing authorization applications in the EU. Several national medicines regulatory agencies have requested EMA to assess the impact of the findings on medicines currently authorized or under evaluation in the EU on the basis of studies performed at the two sites.

► **EMA. Article 31 Review started, 16 December 2017.**

**Chongqing Pharma Research Institute, China (and 11 others)**

**United States of America** – Following an inspection conducted in May 2016, the FDA has warned the active pharmaceutical ingredient manufacturer Chongqing Pharma Research Institute Co. Ltd over data integrity issues. Audit trails from laboratory equipment used to perform high performance liquid chromatography and gas chromatography analyses showed that entire chromatographic sequences and individual injections had been deleted. The FDA investigator was told that it is laboratory practice to perform more injections than required by procedure, and then to delete any undesirable result. Analyses were repeated – without any scientific justification, investigation or documentation of original out-of-specification or otherwise undesirable test results – until acceptable results were obtained. These manipulated test results and incomplete records were used to support batch release decisions.

The FDA has requested the company to respond within 15 days providing details of remedial action.

► **FDA Warning letter No. 320-17-24, 14 February 2017.**

Since the beginning of 2017 the FDA’s Center for Drug Evaluation and Research has issued a total of 12 warning letters to foreign companies, as published on the FDA website as of 8 March. The warnings were issued to five companies based in China, three in India, and two each in Japan and Europe. FDA warning letters are publicly available at [https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/](https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/).
Regulatory news

Vision statement

Japan announces Rational Medicine initiative

Japan – The Pharmaceuticals and Medical Devices Agency (PMDA) has announced its “Rational Medicine” initiative, which aims to serve the best overall interests of the patient through an all-inclusive approach to medicine that is thoroughly based on the latest science and most advanced technology in all relevant areas.

This holistic, patient-centred approach to medicine is intended to advance regulatory science and to create an environment where medical care is strictly evidence-based. To this end, the PMDA plans to continue its initiatives in four areas: (1) innovation through product approval reviews of enhanced rigour and rationality; (2) further promotion of regulatory science; (3) increased sophistication of safety measures through the use of real-world data; and (4) enhanced international partnerships.

Through this approach the PMDA will ensure that patients receive optimal medical treatment, including treatment based on innovative new technologies.


Scientific integrity was also named by the WHO Director-General as one of four priorities that should guide health policies in the next decade. In delivering the keynote address at the 10th anniversary of the University of Washington's Department of Global Health, she said: “Regulatory agencies everywhere must resist the push to replace randomized clinical trials, long the gold standard for approving new drugs, with research summaries provided by pharmaceutical companies. As some argue, making this change would speed up regulatory approval, lower the costs to industry, and get more products on the market sooner. This kind of thinking is extremely dangerous. We must not let anything, including economic arguments or industry pressure, lower our scientific standards or compromise our integrity.”


Pre-market assessment

Ten years of EMA conditional marketing authorizations

European Union – The EMA has published a report on its ten years of experience with conditional marketing authorizations since their introduction in 2006 until June 2016. Thirty products were granted a conditional marketing authorization during that period, and none of them were subsequently revoked or suspended. On average, it took four years to convert the conditional approval into a full marketing authorization based on additional data. The report concludes that conditional marketing authorization enables patients with life-threatening or seriously debilitating conditions to access promising medicines earlier.

The report characterizes the data on which conditional approvals have been granted and the additional data generated through specific obligations. Some areas for improvement are identified, notably with
regard to prospective planning and early
dialogue between stakeholders, including
health technology assessment bodies that
make decisions on reimbursement.

Post-market monitoring

Australia to publish laboratory
testing results

Australia – The TGA has announced that
it will begin publishing the outcomes of its
laboratory testing on its website from mid-
2017.\(^1\) Where products fail any aspect of
testing, details of the test(s) that failed and
outcomes of any follow-up action will also be
provided. Results will be published in May
and November of each year, allowing six
months after the end of each reporting period
for follow-up on any non-compliant findings.

The TGA tests approximately 2000
samples of therapeutic goods annually. The
planned publication of the results is part of
the TGA’s response to a 2015 expert review
of medicines and medical devices regulation,
which had recommended to establish a more
comprehensive post-market monitoring
scheme for medical products in Australia.
Similar information is also published by the
U.S. FDA \(^2\) and the EMA \(^3\).
► \(^1\) TGA Statement, 7 February 2017.

\(^2\) FDA. Drugs > Science & Research (Drugs) >
Drug Quality Sampling and Testing Programs.

\(^3\) EMA website. Human regulatory > Overview >
Compliance > Sampling and testing.

India releases medicines quality
survey results

India – The Central Drug Standards Control
Organization (CDSCO) and the Ministry
of Health and Family Welfare have released
the report of a nationwide medicines quality
survey.

The survey was conducted by the National
Institute of Biologicals and covered the
period 2014-2016. With almost 48000
samples from all major therapeutic
categories collected across the country,
it was the largest-ever such survey to be
conducted in India. A specially designed
in-house software was used for collection,
transmission and analysis of data. Testing
was done at India’s seven Central and three
State Government drug testing laboratories.

Overall the survey found that 3.16% of
samples were not of standard quality, and
0.0245% were spurious drugs.

Of 33656 samples from Indian retail
outlets tested in the survey, 1011 (3%) failed
one or more tests. Dissolution accounted
for a third of the failures, followed by
assay. The list of molecules with the most
non-compliant samples was led by four
antibacterials: erythromycin (28.7%),
gentamicin (21.1%), ceftriaxone (19.8%) and
amikacin (19.5%).

Samples taken at government facilities
had above-average failure rates. Of 8369
samples analyzed, 839 (10%) failed one or
more tests. The most frequently failed tests
were assay and dissolution, followed by
related substances. Non-compliance in the
latter test accounted for about every seventh
failure, occurring almost twice as frequently
as in samples collected at retail outlets.

The highest percentages of non-compliant
samples were seen for bisacodyl (66.7%), zinc
sulfate (51.3%), amikacin (43.3%), oxytocin
(41.3%) and gentamicin (40.2%); ceftriaxone
ranked 9\textsuperscript{th} with 24.6%.

A breakdown by manufacturing units
from which at least 25 samples were tested
showed some particularly high failure rates
in the retail outlet part of the survey: four
sites, including an Indian manufacturing site.
of a well-known multinational company, had failure rates >50%.

Of 4987 samples taken at ports none failed any tests.

Thirteen samples tested in the survey were found to be spurious as defined in Indian legislation. These samples failed to meet the identification test of the labelled drug or had zero active ingredient. The molecules concerned were amoxicillin with or without clavulanic acid (7 samples), prednisolone or methylprednisolone (3 samples), sulfamethoxazole/trimethoprim fixed-dose combination (2 samples) and cefixime (1 sample).


WHO has published guidelines which outline the steps to consider when preparing and conducting a survey of medicines quality. The guidelines provide recommendations and examples of methodological approaches with a discussion of their advantages and disadvantages, and suggestions on how to prepare reports on the results obtained from such surveys. An overview of WHO guidelines on medicines quality is provided in the Norms and standards section (pp. 15-26)


Antimicrobial resistance

(See also page 46: WHO has published its first-ever list of antibiotic-resistant priority pathogens)

Two reports on antimicrobial resistance in Europe

European Union – Experts from the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) have reviewed the measures taken in the European Union (EU) to reduce antimicrobials use in food-producing animals. In their report they emphasize that there is no one-size-fits-all solution. The experts conclude that reducing and replacing antimicrobials can reasonably be assumed to decrease antimicrobial resistance; however, due to lack of data they were unable to quantify the impact of single measures. In addition to reduction measures the experts recommend to rethink the livestock production system and to introduce innovative solutions to prevent and control infectious diseases in animals.


In February 2017 EFSA and the European Centre for Disease Prevention and Control (ECDC) published their annual report on the levels of antimicrobial resistance in food, animals and humans across the EU. The findings underline that antimicrobial resistance remains high and poses a serious threat to public and animal health. Infections caused by bacteria that are resistant to antimicrobials lead to about 25000 deaths in the EU every year. Countries where actions have been taken to reduce, replace and re-think the use of antimicrobials in animals, show lower levels of antimicrobial resistance and decreasing trends.

**Regulatory statement and new guidelines on antibiotic use in India**

India – The Central Drugs Standard Control Organisation (CDSCO) of India has released an advisory statement with recommendations about the rational use of antibiotics to limit antimicrobial resistance. The statement outlines the measures implemented by CDSCO and lists the steps to be taken by other stakeholders. It calls on the regulators of each of India’s States to enforce compliance with laws and regulations and to raise public awareness about the consequences of misuse of antibiotics. The statement further asks the All India Organization of Chemists and Druggists to educate its members on the licensing conditions for medicines sales and cooperate with regulatory authorities, and calls on the pharmaceutical industry to use its network to discourage the sale of antibiotics without a prescription.(1)

In February 2017 the Indian Council of Medical Research (ICMR) released its guidelines on antimicrobial use. As stated in the foreword to the guidelines, an estimated 50% or more of hospital antimicrobial use is inappropriate. The document is intended to guide treatment in order to bring down the burden of antimicrobial resistance in India.(2)

► (1) CDSCO Advisory, 1 February 2017.

**Biosimilars**

**EMA advice on development of biosimilars**

European Union – The EMA will launch a pilot project in February 2017 to test the added value and feasibility of tailored scientific advice for the development of biosimilar medicines. The advice will support the stepwise approach recommended in EU guidelines, where the level and robustness of previously accumulated quality, analytical and functional data should determine the extent and nature of the required studies and tests.

The advice is intended to inform the development strategy for biosimilars. It will not constitute a formal pre-assessment of the data submitted as part of the marketing authorization application.


**FDA guidance on naming of biologicals**

United States of America – The FDA has released its guidance for industry titled *Nonproprietary Naming of Biological Products*. The guidance provides for nonproprietary names to include a core name and a distinguishing FDA-designated suffix that is devoid of meaning and composed of four lowercase letters. The guidance applies to previously licenced and newly licenced originator biological products, related biological products and biosimilar products. FDA is still considering the appropriate suffix format for interchangeable biological products.

In commenting on the guidance at the draft stage, many responders suggested that a meaningful, distinguishable suffix may help to improve pharmacovigilance, enhance safety and facilitate identification between biological products. Some supported the use of a random suffix to avoid creating an unfair advantage for specific manufacturers. Several comments stated that the current practices of FDA and non-FDA entities for identifying products is sufficient for the purpose of pharmacovigilance, and designation of a suffix is not needed.

Regulatory news

Substance use

**Opioid control in Canada**

Canada – Following the launch of the Canadian Drugs and Substances Strategy in December 2016, which reinstates harm reduction as a core pillar of Canada’s drug policy, the Government of Canada has announced new funding of 65 million Canadian dollars (approximately US$ 50 million) over five years to be used to support the federal government’s ongoing implementation of the Opioid Action Plan.\(^{(1)}\)

To raise awareness on the safe use of opioids Health Canada will put forward a regulatory proposal to make warning stickers and patient information handouts mandatory with all opioids dispensed in Canada. The sticker on the medicine container would warn patients about the risks of addiction and overdose with opioid use. The handout would contain broader information on the safe use of opioids and important risks.\(^{(2)}\)


Collaboration

**Landmark EU– U.S. agreement on inspections**

European Union, United States of America – EMA and FDA have agreed to mutually recognize inspections of manufacturing sites for human medicines conducted in their respective territories. This will enable better use of inspection resources with greater focus other parts of the world where there may be greater risk. Around 40% of finished medicines marketed in the EU come from overseas and 80% of the manufacturers of active pharmaceutical ingredients for medicines available in the EU are located outside the Union.

The agreement is an annex to the EU-U.S. mutual recognition agreement which was signed in 1998. Many provisions of the agreement are already effective, and others will enter into force on 1 November 2017. To reach the agreement on inspections the two regulatory authorities have worked together closely since May 2014 and have been auditing and assessing the respective supervisory systems.

\(^\) EMA Press release, 2 March 2017.


**IGDRP roadmap to 2020**

The Steering Committee of the International Generic Drug Regulators Programme (IGDRP) has released the Programme’s Roadmap to 2020. The document describes the five overarching strategic priorities for the initiative as well the key objectives for each of these priorities.

The IGDRP was launched in 2012 as a pilot to increase the efficiency of review procedures for generic medicines and reduce regulatory burden without comprising the safety, efficacy, and quality of products. Availability of quality generic medicines plays an increasingly important role in helping to address rising health care costs.

\(^\) IGDRP News, 21 December 2016.

**IGDRP biowaiver template**

The IGDRP Bioequivalence Working Group has developed a template for biowaiver assessment reports to ensure that the relevant information for a biowaiver is consistently taken into account during assessment, despite the IGDRP members’ differing requirements for biowaivers based on the Biopharmaceutics Classification
System (BCS). As this template can also benefit applicants and the broader regulatory community it has been made available on the IGDRP website.

**ASEAN joint assessment pilot**
The medicines regulatory authorities of the Association of Southeast Asian Nations (ASEAN) have developed a new procedure for joint assessment of marketing authorization applications. The procedure will be implemented, with support and technical advice from WHO, for a pilot period of up to two years starting in January 2017. Participation by applicants and regulators is voluntary for each product to be assessed. The procedure is intended to faster review of priority medicines throughout ASEAN while respecting existing national decision-making processes.

**Under discussion**

**European Union** – The European Commission has invited comments on its revised guidelines on excipients in the labelling and package leaflet of medicinal products for human use. The purpose of the guideline is to define requirements on how excipients must feature on the labelling of medicinal products. The original guidance was adopted in 2003.

**European Union** – The EMA has launched a public consultation on the proposed revision to its 2010 policy on access to documents. The new version extends the scope of the policy to include explicitly corporate documents and takes into account the move towards more transparency that has led to the publication of additional documents on the EMA website since 2010.

**European Union** – The EMA has released a concept paper on developing a guideline on quality requirements of medicinal products containing a device component for delivery or use of the medicinal product. Such requirements are intended for situations where a medicinal product is used along with a specified medical device, and there is no intention to duplicate the CE marking process for medical devices.

**United States of America** – The FDA has released three texts regarding different types of manufacturers’ communications about medical products, including: communications with funders and similar entities, communications conveying content that is not included in the product information; and communications on unapproved uses of approved products.

**New Zealand** – Medsafe has launched a public consultation on labelling requirements for over-the-counter miconazole products to include a compulsory warning about
Under discussion

a known interaction with warfarin. The revision is proposed because potentially life-threatening events continue to be reported in New Zealand in patients taking the two medicines concomitantly.

► Medsafe Advice, 15 February 2017.
Closing date: 13 April 2017.

United Kingdom – The MHRA is developing a strategy for the creation of pharmacopoeial public quality standards for biological medicines and has launched a consultation to seek input on the strategy, and on how the standards are used and can be improved.

► MHRA Open consultation, 9 January 2017.
Closing date: 10 April 2017.

Australia – The 2015 Review of Medicines and Medical Devices Regulation in Australia included three recommendations to improve access to unapproved therapeutic goods through changes to existing schemes. The recommendations made are to decrease duplication of work and to streamline access to unapproved therapeutic goods considered to have an established history of use.

► TGA Consultation, 15 February 2017.
Consultation closed 29 March 2017.

Australia – The TGA has released a consultation paper on reforms to its complementary medicines regulation. The document proposes a three-tiered risk-based framework, introducing a new assessment pathway sitting between the existing pathways for listed medicines (low risk) and registered medicines (high risk).

Consultation closed 28 March 2017.

United States of America – The FDA has published its draft guidance on the data and information expected for a biological product to meet the standard for interchangeability. The availability of biosimilar and interchangeable products will provide more treatment options, potentially driving down costs to give more patients access to needed medicines.

Consultation closed 20 March 2017.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has released its reflection paper on Good Clinical Practice (GCP) Renovation. The paper proposes a revision of the ICH E8 General Considerations for Clinical Trials, as well as further revisions to the E6 Guideline for GCP.

Consultation closed 11 March 2017.

European Union – The EMA has published a summary of ideas on advanced therapy medicinal products (ATMP) put forward at a May 2016 workshop. While revisions to the legislation on ATMPs in Europe are currently not foreseen, the workshop outcomes will be considered for a wider EU plan to be developed.


European Union – In response to a European Commission consultation on the development of good manufacturing practice (GMP) guidelines for ATMPs,(1) the Pharmaceutical Inspection Cooperation Scheme (PIC/S) has expressed its concern about proposed lowered GMP standards for ATMPs, leading to an internationally non-harmonized approach in this area.(2)

► (1) EC. Summary of the responses to the targeted stakeholder consultation.
## Approved

### Plecanatide for chronic idiopathic constipation

**Product name:** Trulance®

**Dosage form:** Tablets

**Class:** Guanylate cyclase-C agonist, human uroguanylin analog

**Approval:** FDA

**Use:** Treatment of chronic idiopathic constipation (CIC) in adults.

**Benefits:** Additional treatment option for adult patients with CIC.

**Safety information:** Plecanatide should not be used in children under six years due to the risk of serious dehydration. Its use should be avoided in patients aged 6-18 years, as its safety and effectiveness have not been established in these patients. The product should not be used in patients with known or suspected mechanical gastrointestinal obstruction. The most common and serious side effect was diarrhoea. If severe diarrhoea occurs, patients should stop taking the medicine and contact their health care provider.


### Telotristat ethyl for carcinoid syndrome diarrhoea

**Product name:** Xermelo®

**Dosage form:** Tablets

**Class:** Serotonin synthesis inhibitor

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

**Use:** Adjunctive treatment of carcinoid syndrome diarrhoea in adults when the condition is inadequately controlled with somatostatin analog therapy alone.

**Benefits:** Inhibits the production of serotonin by carcinoid tumours and reduces the frequency of carcinoid syndrome diarrhoea.

### Parathyroid hormone replacement therapy

**Product name:** Natpar®

**Dosage form:** Injection

**Class:** Hormone; **ATC code:** H05AA03

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

**Use:** Adjunctive treatment of patients with chronic hypoparathyroidism who cannot be adequately controlled with calcium and vitamin D

**Benefits:** Ability to reduce the need for calcium and vitamin D supplements while maintaining adequate serum calcium levels.
### Approved

**Note:** This is the first EMA-approved hormone replacement therapy for parathyroid disorder.


### Rucaparib for certain ovarian cancers

**Product name:** Rubraca®

**Dosage form:** Tablets

**Class:** Poly ADP-ribose polymerase (PARP) inhibitor; *ATC code:* L01XX55 (temporary)

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

**Use:** Treatment of advanced ovarian cancer in women who have been treated with two or more chemotherapies and whose tumours have a specific gene mutation (deleterious BRCA) as identified by an FDA-approved companion diagnostic test.

**Benefits:** Additional treatment option for women with BRCA-mutated ovarian cancer.

**Safety information:** Serious risks associated with rucaparib include myelodysplastic syndrome, acute myeloid leukaemia and foetal harm.


### Nusinersen for spinal muscular atrophy

**Product name:** Spinraza®

**Dosage form:** Injection

**Class:** Survival motor neuron-2 (SMN2)-directed antisense oligonucleotide

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

**Use:** Treatment of adults and children with spinal muscular atrophy (SMA)

**Benefits:** Improvement in motor functions such as head control, sitting, ability to kick in supine position, rolling, crawling, standing and walking.

**Notes:** This is the first medicine approved in the U.S. for the treatment of SMA, a rare and often fatal hereditary condition affecting muscle strength and movement. According to an article in the New York Times, treatment could cost US$ 625,000-$750,000 in the first year, and about $375,000 annually after that.


### Sublingual dust mite allergen extract

**Product name:** Odactra®

**Dosage form:** Sublingual tablet

**Class:** Allergen

**Approval:** FDA

**Use:** Treatment of house dust mite-induced allergic rhinitis.

**Benefits:** Reduction in allergy symptoms

**Safety information:** Boxed warning about the risk of severe allergic reactions, some of which can be life-threatening. As with all sublingual allergen extracts, patients should be prescribed auto-injectable epinephrine (adrenaline).


### Sodium zirconium cyclosilicate for hyperkalaemia

**Product name:** Lokelma®

**Dosage form:** Powder for oral suspension; *ATC code:* V03AE10

**Approval:** EMA/CHMP recommendation

**Use:** Treatment of hyperkalaemia in adult patients.

**Benefits:** Ability to lower serum potassium levels.

Two adalimumab biosimilars

Product name: Amgevita®  
Reference product: Humira®  
Approval: EMA recommendation  

Product name: Solymbic®  
Reference product: Humira®  
Approval: EMA recommendation  
Use: Treatment of rheumatoid arthritis, enthesitis-related arthritids, axial spondyloarthritis, psoriatic arthritis, psoriasis, hidradenitis suppurativa, Crohn's disease, ulcerative colitis and uveitis.  

Three clinically important generics approved in China

The China Food and Drug Administration (CFDA) has announced the approval of three clinically important generics manufactured by Chinese companies, as well as the active pharmaceutical ingredients contained in the products. The medicines concerned are the anti-cancer medicine gefitinib and the antiretrovirals efavirenz and tenofovir disoproxil fumarate (TDF). TDF can also be used to treat hepatitis B.  
(3) RAPS. Asia Regulatory Roundup. 3 January 2017.

Two tests for guiding antibiotic use

The FDA has cleared two tests that can help to guide the use of antibiotics. The Vidas Brahms PCT Assay was cleared for expanded use in guiding treatment in lower respiratory tract infections, in addition to its use in sepsis. The test measures procalcitonin (PCT), a protein associated with the body's response to a bacterial infection. It is intended to be used in the hospital or emergency room setting. The FDA also cleared the PhenoTest BC Kit, which can identify various infective agents causing bloodstream infections and provide sensitivity results for selected antibiotics.  
► (1) FDA News release, 23 February 2017.  
(2) FDA News release, 23 February 2017.

Extension of indications

Elvitegravir & cobicistat & emtricitabine & tenofovir for children over 12 years of age

Product name: Stribild®  
Approval: FDA  
Newly approved use: Treatment of HIV in children over 12 years of age weighing at least 35 kg.  
Publications and events

Research and development

WHO publishes priority list of antibiotic-resistant pathogens

Geneva – WHO has published its first-ever list of antibiotic-resistant “priority pathogens” that pose the greatest threat to human health. The list was drawn up in a bid to guide and promote research and development (R&D) of new antibiotics, as part of WHO’s efforts to address growing global resistance to antimicrobial medicines. The issue of antimicrobial resistance is to be brought to the attention of the G20 health experts at their meeting in Berlin in early March 2017.

The list is reproduced below. It highlights in particular the threat of gram-negative bacteria that are resistant to multiple antibiotics.

**WHO priority pathogens list for R&D of new antibiotics**

**Priority 1: CRITICAL**
- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

**Priority 2: HIGH**
- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalexin-resistant, fluoroquinolone-resistant

**Priority 3: MEDIUM**
- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

Tuberculosis – whose resistance to traditional treatment has been growing in recent years – was not included because it is targeted by other, dedicated programmes.\(^1\)

WHO has stressed the urgent need for R&D for drug-resistant tuberculosis in a separate statement.\(^2\)

\(^1\) WHO News release, 27 February 2017. WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Publication date: 27 February 2017.


Access to medicines

**Intellectual property rules amended to ease global access to medicines**

Geneva – An amendment to the WTO Trade Related Aspects of Intellectual Property Rights (TRIPS) Agreement entered into force on 23 January 2017, securing for developing countries a legal pathway to access affordable medicines under WTO rules. As two-thirds of the WTO members have ratified the amendment, the threshold has been reached which was needed to formally amend the TRIPS Agreement. The amendment empowers importing developing and least-developed countries facing public health problems and lacking the capacity to generic medicines to seek such medicines from third country producers under compulsory licensing arrangements.

\(\text{World Trade Organization News, 23 January 2017.}\)
OECD reports on health spending and new technologies

London – The Organisation for Economic Co-operation and Development (OECD) has launched two reports that show how pharmaceutical spending is increasingly skewed towards high-cost products and technologies, with little or no benefits for people’s health. In some cases there is even a risk of worse health outcomes.

The first report recommends strategies for countries to spend significantly less on health care while maintaining health system performance and health outcomes. The second report provides analyses on the adoption and impact of medical technology and identifies opportunities to optimize their use in health systems. It discusses the need for an integrated and cyclical approach to managing health technology in order to mitigate clinical and financial risks and ensure acceptable value for money. A new governance framework is proposed to address current challenges faced by policymakers.

Calls for changes to European Commission’s R&D programme

Amsterdam – Health Action International has released a joint position paper calling upon the European Commission to make substantial changes to how it funds research and development (R&D) projects for new medicines to allow for greater public access. The paper highlights the EU’s responsibility to ensure public returns on its R&D investments, reducing the major inequalities that persist in the quality of healthcare available in EU Member States.

The call comes after the Commission’s public consultation for the mid-term review of the European Union’s (EU) Research and Innovation programme, Horizon 2020, which administers a funding pool of nearly €80 billion. At a time when there is general concern over high prices for new medicines such as cancer and hepatitis C products, the joint paper has been endorsed by many humanitarian groups.

Using human rights law to support access to medicines

Two recent articles highlight the human rights approach to reimbursing expensive medicines. In the first article, the authors argue that while all patients have an equal right to access essential medicines, the order and timing of its fulfilment is gradual. This justifies ranking treatments for reimbursement, with more cost-effective treatments being included first. The second article looks at thirteen national constitutions that include a state duty to provide access to essential medicines as part of the right to health. Nine of these constitutions were amended or adopted after 2008. The research was conducted under a collaboration between the Medical Centre and the Faculty of Law at the University of Groningen in the Netherlands.
First MPP licence for anti-tuberculosis medicine

Geneva – The Medicines Patent Pool (MPP) has signed a licence with Johns Hopkins University to facilitate the clinical development of sutezolid, an investigational antibiotic that has shown promise in the treatment of both drug-sensitive and drug-resistant tuberculosis. The exclusive, royalty-free licence covers all countries that have patents issued or pending for a combination therapy comprising sutezolid and two additional anti-tuberculosis medicines. The patent for sutezolid expired in 2014, but the patent for the use of sutezolid in combination therapy for tuberculosis – held jointly by Pfizer Inc and Johns Hopkins University – is valid until August 2029 in the countries in which it was filed.\(^{(1)}\)

Public health groups have welcomed the move but warn that the deal lacks safeguards that would ensure worldwide affordability. They have also called on Pfizer and Sequella, who hold secondary patents and clinical data on sutezolid, to provide open access to all existing data.\(^{(2)}\)


Papillomavirus vaccine review documents published

A paper published in the Indian Journal of Medical Ethics makes available the procedural documents that were used in the EMA’s review of human papillomavirus (HPV) vaccine. The review, which was completed in November 2015, found that there was no evidence of an association between the HPV vaccines and two dysautonomic syndromes (complex regional pain syndrome and postural orthostatic tachycardia syndrome), despite the existence of independently clustered reports (signals). The paper reveals the process that led to the conclusions of the EMA review.

► Jefferson T, Jørgensen L. Human papillomavirus vaccines, complex regional pain syndrome, postural orthostatic tachycardia syndrome, and autonomic dysfunction – a review of the regulatory evidence from the European Medicines Agency [Published online]. IJME. 2016; 2 (1 (NS)), 30.

New CIOMS guide on active vaccine surveillance

Geneva – The Council for International Organizations of Medical Sciences (CIOMS) has announced the publication of its Guide to Active Vaccine Safety Surveillance. The Guide addresses the situation facing national immunization programmes and regulatory authorities when a new vaccine is being introduced and vaccine safety needs to be assured. It offers a structured process for evaluating whether significant knowledge gaps exist, whether passive safety surveillance is adequate, and if not, how active vaccine safety surveillance studies can be designed and implemented.

With novel vaccines on the horizon, many of which are likely to be introduced early and/or exclusively into countries with limited pharmacovigilance experience and infrastructure, there is an urgent need for guidance on generating reliable post-licensure safety assessment data.

**Measuring pharmaceutical systems strengthening**

A recently published review article highlights the importance of policy, laws and governance as the central hub for an efficient and equitable system, with medicines regulatory functions to ensure the safety, efficacy and quality of pharmaceutical products and related services. The article proposes definitions for a pharmaceutical system and proposes seven components to measure pharmaceutical systems strengthening: (1) pharmaceutical products and related services; (2) policy, laws and governance; (3) regulatory systems; (4) innovation, research and development, manufacturing, and trade; (5) financing; (6) human resources; and (7) information.


**Spotlight on flawed bioequivalence trials in India**

Hyderabad – An online Reuters article has highlighted the dangers of “India’s flawed generic drugs trials business”. More than a dozen volunteers interviewed by Reuters across four Indian cities said that they participated in as many studies as possible to earn money, waiting much less than the internationally recommended 90 days between trials. This waiting period is needed to protect the health of study participants and ensure the validity of the trial data.

In recent years, there has been increasing concern about the integrity of data generated at Indian contract research organizations. In 2015, the EMA suspended more than 700 generic products because of issues with the bioequivalence data submitted in support of their marketing authorization applications.


**Medicines use**

**Over- and underuse of health care interventions**

A series of articles published in *The Lancet* shows that underuse of proven medical care and overuse of unproven services exist side by side in all economic settings, causing suffering to millions of people as well as wasteful misallocation of resources for society.

In the final paper of the series the authors argue that overuse and underuse are symptoms of a health-care system that does not reflect the ethics of medicine and that, with universal health coverage adopted as a target under the UN Sustainable Development Goals, focusing the world’s attention on achieving the right care is both an urgent task and an enormous opportunity.

The authors conclude that the deepest drivers of poor care arise out of fundamental inequalities of information, wealth and power. The path to the right care will therefore require more data on medicines use, a deeper understanding of care delivery as a science, political consensus for redirecting investments towards new, more balanced delivery models, and leadership from clinicians to create an activated, informed and mobilized citizenry.

A comment to the series points out that WHO and other bodies have courageously led moves to increase patient safety and to reduce inappropriate use of antimicrobial agents, and that they should also engage in promoting strategies to reduce the overuse of ineffective care.

Disease updates

Malaria: global targets jeopardized

Geneva – WHO has released its *World Malaria Report 2016*. According to the report, there were 212 million new cases of malaria and 429 000 deaths worldwide in 2015. Ten countries and territories reported fewer than 150 indigenous cases of malaria, and a further nine countries reported between 150 and 1000 cases. Kyrgyzstan and Sri Lanka were recently certified by WHO to have eliminated malaria, having achieved at least three consecutive years of zero indigenous cases.

Sub-Saharan Africa accounted for 90% of malaria cases and 92% of malaria deaths in 2015. Children under five years accounted for an estimated 70% of all malaria deaths globally. The report shows that children and pregnant women in sub-Saharan Africa have greater access to effective malaria control, with a steep increase in diagnostic testing for children and preventive treatment for pregnant women reported over the last five years.

Funding shortfalls and fragile health systems are undermining overall progress, jeopardizing the attainment of the targets defined in the Global Technical Strategy for Malaria 2016-2030. Funding has flat-lined since 2010, totalling US$ 2.9 billion in 2015 or 45% of the 2020 funding milestone.


Ebola: vaccine shown to be effective

Geneva – The results of a clinical trial conducted in Guinea on the rVSV-ZEBOV Ebola vaccine have been published in *The Lancet*. The trial was led by WHO, together with Guinea’s Ministry of Health, Médecins sans Frontières and the Norwegian Institute of Public Health, in a unique collaboration with international partners. Its findings confirm that the vaccine is safe and provides high protection against the disease. Additional studies are ongoing to provide more data on the safety of the vaccine in children and other vulnerable populations such as people with HIV.

In January, GAVI, the Vaccine Alliance provided US$5 million to Merck towards the future procurement of the vaccine once it is approved, prequalified and recommended by WHO. As part of this agreement, Merck committed to ensure that 300 000 doses of the vaccine are available for emergency use in the interim, and to submit the vaccine for licensure by the end of 2017. Merck has also submitted the vaccine to WHO’s Emergency Use and Assessment Listing procedure (EUAL).

The rapid development of rVSV-ZEBOV contributed to the development of WHO’s R&D Blueprint, a global strategy to fast-track the development of effective tests, vaccines and medicines during epidemics.


Polio: public health emergency continues

Geneva – The Emergency Committee under the International Health Regulations (2005) (IHR) unanimously agreed that the international spread of poliovirus remains a Public Health Emergency of International Concern (PHEIC). At the recommendation of the Committee, the WHO Director-General extended the Temporary Recommendations for a further three months. The recommendations aim mainly at raising political awareness and official recognition of the emergency, ensuring strategic vaccination of people...
at risk with documentation of people’s vaccination status, and maintaining surveillance and detection measures. The importance of regional cooperation and cross-border coordination was emphasized. The Committee urged all countries to avoid complacency which could easily lead to a polio resurgence.


Cancer: WHO calls for early diagnosis
Geneva – Ahead of World Cancer Day 2017, WHO has released new guidelines aiming to improve early diagnosis of cancer and ensure prompt treatment, especially for breast, cervical, and colorectal cancers. Treatment of cancer at an early stage is generally more effective, less complex and less expensive. Low- and middle-income countries tend to have the greatest challenges in providing effective diagnostic and treatment services. WHO encourages these countries to prioritize basic, high-impact and low-cost services and to reduce the need for out-of-pocket payment for these services to increase their uptake.(1)

According to new WHO figures cancer caused 8.8 million deaths in 2015, making it the second leading cause of death globally. Two thirds of cancer deaths occur in low- and middle-income countries. In 2010, the global economic cost of cancer through healthcare expenditure and loss of productivity was estimated at US$ 1.16 trillion. Approximately 14 million new cases occurred in 2012, and the incidence is expected to rise by about 70% over the next two decades.(2)

WHO matters

WHO data portal on health coverage
Geneva – WHO has launched a new data portal to track progress towards universal health coverage. The portal features the latest data on access to health services globally and in each of WHO’s 194 Member States, along with information about equity of access. Next year WHO will add data on the impact that paying for health services has on household finances.

Universal health coverage is essential to achieving the targets of the Sustainable Development Goal (SDG) for good health and well-being, which will in turn support other SDGs. The portal highlights the areas where governments need to act to strengthen their health systems. For example it shows that less than half of children with suspected pneumonia in low income countries are taken to an appropriate health provider, that 44% of WHO Member States report having less than one physician per 1000 population, and that the African Region has only 3% of the world’s health workers although it bears almost 25% of the global burden of disease.


WHO Director-General supports new prequalification funding model
Geneva – The WHO Director-General expressed her support for the new financing arrangements, announced in September 2016, that are intended to make WHO Prequalification sustainable in the future. In her report to the WHO Executive Board she stated: “The programme is one of our most successful initiatives. It has transformed the market for public health vaccines and other medical products, making supplies more abundant and predictable and prices more

(1) WHO. News release, 3 February 2017.
affordable. In addition, the new financing model is designed to ensure equity among manufacturers, with provisions included to enable small manufacturers that meet quality standards to enter the market on an equal footing with large companies.”

► WHO. Report by the Director-General to the Executive Board at its 140th session. 23 January 2017.

**New medicines invited for prequalification**

**Geneva** – The WHO Prequalification Team–Medicines (PQT) has published new invitations for expression of interest (EOI) for product evaluation. In the area of reproductive health the newly eligible products include benzathine benzylpenicillin and procaine benzylpenicillin injectables. Products added for neglected tropical diseases include miltefosine capsules, injectable sodium stibogluconate, injectable paromomycin as well as azithromycin tablets. The respective active pharmaceutical ingredients (API) have been added to the EOI for APIs. Details are found in the EOIs listed below, available on the WHO prequalification website.

► WHO PQT. 8th EOI for Reproductive Health. 22 December 2016.
WHO PQT, 5th EOI for Neglected Tropical Diseases. 9 February 2017.
WHO PQT, 12th EOI for APIs. 27 December 2016.
WHO PQT, 13th EOI for APIs. 15 February 2017.

**Upcoming events**

**2017 joint UNICEF–UNFPA–WHO manufacturers meeting**

The 2017 joint UNICEF–UNFPA–WHO manufacturers meeting will take place in Copenhagen, Denmark, on 18–21 September 2017. Due to a clash of meeting events it was not possible to hold a joint UNICEF–UNFPA–WHO meeting in 2016.

The joint manufacturers meeting provides information for suppliers of medical products for use by UN agencies and other international organizations.

► WHO Prequalification website. Events.

**New WHO prequalification website**

**Geneva** – The WHO Prequalification Team–Medicines has released its new website. The site has been reshaped to streamline the content, improve navigation and enhance data retrieval and search features. Greater use is also made of visual elements.

The new website is the result of close collaboration with manufacturers, regulators, procurers, quality control laboratories and health workers and other stakeholders. Feedback was sought before the launch, and is still invited as a basis for further improvements if warranted. The websites of the prequalification workstreams for vaccines and diagnostics will also be reviewed and updated.

► WHO. Essential Medicines and Health Products: Prequalification of medicines [website]. https://extranet.who.int/prequal
Consultation documents

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

The International Pharmacopoeia

Ganciclovir
(Ganciclovirum)

This is a draft proposal of a monograph for The International Pharmacopoeia (Working document QAS/16.652, January 2017).

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

Molecular formula. C₉H₁₃N₅O₄

Relative molecular mass. 255.23

Graphic formula

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

Description. White or almost white, crystalline powder.

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

Category. Antiviral (Purine nucleoside analogue).

Storage. Preserve in well-closed containers. Protect from light and moisture.

Additional information. Ganciclovir is hygroscopic and may exhibit polymorphism.
Requirements

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

**Identity tests**

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

A. Carry out the test as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from ganciclovir RS or with the reference spectrum of ganciclovir. If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and ganciclovir RS in a small amount of hot water R (80°C), allowing to cool in an ice-bath, filtering and drying the precipitate at 105°C for 3 hours. The infrared absorption spectrum is concordant with the spectrum obtained from ganciclovir RS.

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

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

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

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

D. Dissolve about 5 mg of the sample in 500 mL of water R. The absorption spectrum (1.6) of this solution, when observed between 200 nm and 300 nm, exhibits a minimum at about 222 nm and maximum at about 252 nm with a shoulder at about 275 nm.
**Clarity and colour of solution.** Dissolve 1.25 g in sodium hydroxide (~40 g/L) TS and dilute to 25 mL. This solution is clear and not more intensely coloured than reference solution Y5, when compared as described under 1.11.2 Degree of coloration of liquids, Method II.

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

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

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

**Water.** Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using 0.3 g of the substance and methanol as solvent. The substance to be examined has a limited solubility in methanol and will appear as a slurry. Replace the solvent after each titration. The water content is not more than 40 mg/g.

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

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

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

Prepare the following solutions using mobile phase as a diluent. For solution (1) dissolve about 30 mg of the test substance using sonication and dilute to 50.0 mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 1.0 mL of this solution to 10.0 mL. For solution (3) dissolve 3.0 mg of ganciclovir RS using sonication and dilute to 5.0 mL. For solution (4) dissolve the content of a vial of ganciclovir for system suitability RS (containing the impurities A, B, C, D, E and F) in 1.0 mL of solution (3).

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

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

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

¹ A Thermo BioBasic SCX column (4.6 mm × 250 mm, 5 μm) has been found suitable.
In the chromatogram obtained with solution (1):

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

**Assay.** Dissolve about 0.2 g, accurately weighed, in 10 mL of anhydrous formic acid R and dilute to 60 mL with anhydrous glacial acetic acid R. Titrate with perchloric acid (0.1 mol/L) VS, determining the end-point potentiometrically as described under 2.6 Non-aqueous titrations. Carry out a blank titration. Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 25.52 mg of ganciclovir (C₉H₁₅N₅O₄).

**Impurities**

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

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

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

and enantiomer

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

\[
\begin{align*}
\text{HN} & \quad \text{N} \\
\text{HN} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

and enantiomer

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

\[
\begin{align*}
\text{HN} & \quad \text{N} \\
\text{HN} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

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

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


**New reference substances**

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

**New reagent**

Aciclovir R
Aciclovir of a suitable quality should be used.

***
Ganciclovir for injection
(Gancicloviri ad injectionem)

This is a draft proposal of a monograph for The International Pharmacopoeia (Working document QAS/16.653, January 2017).

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

Description. A white powder or loose lumps.

Category. Antiviral (Purine nucleoside analogue).

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

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

Ganciclovir for injection is hygroscopic.

Requirements

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

Definition. Ganciclovir for injection is a freeze-dried powder prepared by the neutralization of Ganciclovir with the aid of sodium hydroxide. Ganciclovir for injection contains not less than 90.0% and not more than 110.0% of the labelled amount of ganciclovir (C$_9$H$_{13}$N$_5$O$_4$).

Identity tests

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

A. Dilute a quantity of the test substance, containing the equivalent of about 0.2 g of Ganciclovir with 10 mL water R. Adjust the suspension to pH 6–7 with hydrochloric acid (0.1 mol/L) TS and allow to stand for 30 minutes. Filter the suspension, wash the filtrate with 20 mL water R and dry it at 105°C for 3 hours. Carry out the test as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the reference spectrum of ganciclovir or with the spectrum obtained from ganciclovir RS treated similarly. If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the dried filtrate and ganciclovir RS in a small amount of hot water R (80°C), allowing to cool in an ice-bath, filtering and drying the precipitate at 105°C for 3 hours. The infrared absorption spectrum is concordant with the spectrum obtained from ganciclovir RS.

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

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

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

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

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

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

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

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using 0.3 g of the substance and methanol as solvent. The substance to be examined has a limited solubility in methanol and will appear as a slurry. Replace the solvent after each titration. The water content is not more than 30 mg/g.

Related substances. Carry out the test as described under 1.14.4 High performance liquid chromatography using the conditions given under “Assay”.
Prepare the following solutions using mobile phase as a diluent. For test solution (1) dissolve using sonication a quantity of the powder for injection, containing the equivalent of about 30 mg ganciclovir, and dilute to 50.0 mL. For solution (2) dilute 1.0 mL of solution (1) to 100 mL. Dilute 1.0 mL of this solution to 10.0 mL. For solution (3) dissolve using sonication 3.0 mg of ganciclovir RS and dilute to 5.0 mL. For solution (4) dissolve the content of a vial of ganciclovir for system suitability RS (containing the impurities A, B, C, D, E and F) in 1.0 mL of solution (3).

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

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

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

In the chromatogram obtained with solution (1):
- the area of any peak corresponding to impurity F, when multiplied by a correction factor of 0.7, is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

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

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

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

Weigh and mix the contents of 5 containers. Prepare the following solutions in mobile phase. For solution (1) dissolve a quantity of the powder of injection, equivalent to about 30 mg of ganciclovir, accurately weighed, and dilute to 50.0 mL. Dilute 10.0 mL of this solution to 100.0 mL. For solution (2) dissolve 15.0 mg of ganciclovir RS, and dilute to 25.0 mL. Dilute 10.0 mL of this solution to 100.0 mL.

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

Measure the areas of the peaks corresponding to ganciclovir in the chromatograms of solution (1) and (2) and calculate the percentage content of ganciclovir \( (C_{\text{H}_13\text{N}_5\text{O}_4}) \) per container, using the declared content of \( C_{\text{H}_13\text{N}_5\text{O}_4} \) in ganciclovir RS.

**Bacterial endotoxins.** Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 0.50 IU of endotoxin per mg of ganciclovir.

**Impurities**
- The impurities limited by the requirements of this monograph include impurity B listed in the monograph on Ganciclovir.

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