

# WHO Drug Information

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**18<sup>th</sup> International Conference of Drug Regulatory Authorities (ICDRA)**

The 18<sup>th</sup> ICDRA will be hosted by the Health Products Regulatory Authority (HPRA) of Ireland and the World Health Organization

Dublin, Ireland, 3–7 September 2018  
<http://www.icdra2018.ie/>

**Abbreviations and websites**

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

**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 websites referenced.

# Regulatory networks

## Update on the WHO-National Control Laboratory Network for Biologicals

**WHO prequalifies vaccines for use in Member States. In 2016 WHO initiated the establishment of a Network of national control laboratories (NCLs) that test prequalified vaccines. The Network aims to reduce redundant lot release testing and contribute to more cost-effective testing, thereby improving overall regulatory oversight and reducing regulatory burden. An article about the Network was included in [Issue 1 \(2017\)](#) of this journal.**

**At the end of 2017 the Network held its First General meeting, which marked the move to the operational stage. This paper provides an update on achievements and next steps.**

### Background

WHO prequalifies vaccines for procurement by UNICEF, the PAHO Revolving Fund and GAVI among others.<sup>1</sup> Prequalified vaccines are used to immunize approximately two thirds of the global birth cohort each year.<sup>(1)</sup> A condition for acceptance of prequalification applications for a vaccine is that the national regulatory authority (NRA) responsible for its oversight has passed a WHO assessment of defined vaccine-related functions,<sup>(2)</sup> including the evaluation of vaccine batches before they are released onto the market.<sup>(3)</sup>

Testing of vaccines is complex and expensive. The NCLs responsible for lot release of prequalified vaccines have in-depth experience with regulatory

testing of the products. Each year they test thousands of lots against approved specifications. Once a lot has been released by the responsible NCL, and provided that it is shipped and stored under appropriate safe conditions, it can be considered to meet its specifications. WHO guidelines therefore recommend that regulatory authorities should use risk-based testing approaches and should consider relying on the outcomes of the lot release done by other regulators.<sup>(3)</sup>

An example of such reliance is the approach used in Europe, where by law each vaccine lot may be tested only once through the Official Control Authority Batch Release (OCABR) before being marketed in countries of the EU and the European Economic Area<sup>2</sup>.

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<sup>1</sup> List of prequalified vaccines available at: [https://extranet.who.int/gavi/PQ\\_Web/](https://extranet.who.int/gavi/PQ_Web/)

<sup>2</sup> Council of Europe. Batch Release for Human Biologicals: Vaccines, blood and plasma derivatives. See: <https://www.edqm.eu/en/batch-release-human-biologicals-vaccines-blood-and-plasma-derivatives>

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This update is based on the report of the First General Meeting of the WHO-NNB Network, held in Noida, India, on 31 October –2 November 2017. We thank Mr Mike Ward, Coordinator, WHO Regulatory Systems Strengthening (RSS) Team, for helpful comments on the manuscript. Contact Dr Ute Roskopf ([rosskopfu@who.int](mailto:rosskopfu@who.int)) for further information.

## Update on the WHO-NCL Network for Biologicals

Globally however, as the number and capacity of NCLs have increased, the same vaccine batches are often re-tested in multiple recipient countries. This is causing unnecessary delays in supply and sometimes leads to rejection of lots that do actually meet specifications, due to differences in testing methods.

To reduce redundant testing and facilitate access to prequalified vaccines, WHO therefore initiated the establishment of the WHO National Control Laboratory Network for Biologicals in 2016.<sup>3</sup> An update on progress is provided below.

### Progress update

#### Advocacy

The Network was discussed at the 17<sup>th</sup> International Conference of Drug Regulatory Authorities (ICDRA), leading to two formal recommendations:

- (To WHO:) *Establish a global network of national vaccine control laboratories involved in testing of WHO-prequalified vaccines.*
- (To Member States:) *For efficient lot release testing of vaccines, consider a risk-based approach or networking (reliance) approach.*<sup>(4)</sup>

Information about the Network was also presented to the WHO Expert Committee on Biological Standardization (ECBS), which sets the global standards that underpin WHO prequalification of vaccines.

#### Network membership

The Network's terms of reference and the participation and confidentiality agreement, were finalized with input from the WHO legal department. The NCLs of the

following countries have formalized their participation:

- Full members (responsible for testing of one or several prequalified vaccines): Australia, Belgium, Bulgaria, Cuba, Denmark, France, Germany, India, Indonesia, Italy, Senegal, South Africa, Switzerland, Thailand, the Netherlands and the United Kingdom. Agreements with the NCLs of Brazil, Canada, China, the Republic of Korea, Russia and Sweden were pending signature at the time of writing.
- Associate members (importing prequalified vaccines): Bangladesh, Hungary and Sri Lanka. The authority of Bhutan is expected to join in the near future, and the authority of Ghana is considering to become a Network member.

Going forward it is envisaged that regulatory authorities of all WHO Member States will participate in this Network, which offers a pathway for mutual recognition and reliance at the global level.

#### General Network meetings

One of the two main routes of Network operations is through regular face-to-face meetings. In 2017 the Network held its First General Meeting in Noida, India. The meeting was hosted by the National Laboratory of Biologicals (NIB) of India and organized by WHO. Representatives from 20 of the 24 NCLs currently testing WHO-prequalified vaccines, manufacturers and other stakeholders participated. The meeting marked the move to the Network's operational stage. Funding from the Bill & Melinda Gates Foundation for the meeting is gratefully acknowledged.

One day of each general meeting is devoted to technical sessions on sharing best practice. The topics at the First General Meeting were the design and interpretation

<sup>3</sup> Meeting report available at [http://www.who.int/immunization\\_standards/vaccine\\_quality/who\\_rivm2016/en/](http://www.who.int/immunization_standards/vaccine_quality/who_rivm2016/en/)

of control charts, and handling out-of-specification results.

Preparations are ongoing for the Second General Meeting of the Network, to be held in Rome, Italy, on 25–27 September 2018. The meeting will be hosted by the Centro Nazionale per il Controllo e la Valutazione dei Farmaci / Istituto Superiore di Sanità (CNCV/ISS).

### Information-sharing

The other main route of Network operations is information-sharing through a password-protected platform hosted on a WHO server. An early pilot version was demonstrated at the First General Meeting. Development is ongoing. Once the platform is operational, WHO and NCLs will upload and maintain relevant information on an ongoing basis.

### Update on the WHO-NCL Network for Biologicals

The platform will host the following main types of information:

- **Laboratory profiles:** As agreed in 2016, the participating NCLs have completed a systematic mapping of their set-up and lot release systems and activities. Twenty such laboratory profiles were sent to WHO ahead of the First General Meeting and were subsequently shared among all contributing NCLs. The laboratory profiles are currently being uploaded to the subsites of the member NCLs on the information-sharing platform (*Box 1*), for an initial round of validation by test users from NCLs.
- **Outcomes of WHO lot testing:** WHO tests vaccines as part of the prequalification process and implements a targeted testing plan of prequalified vaccines supplied to UN-funded

#### Box 1:

#### Example of a NCL subsite on the pilot version of the WHO-NNB electronic platform

WHO Online Workspace

World Health Organization  
National Control Laboratory Network for Biologicals

Belgium

Scientific Institute of Public Health

sciensano  
Quality of Vaccines and Blood Products

Contracted by WHO for technical testing of vaccines  
Contracted by WHO for sharing of lot release information  
Lot release for Belgian and European market  
Quality Assurance Standard: ISO/IEC 17025 and ISO/IEC 9001  
Related national regulatory authority: Federal Agency for Medicines and Health Products

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## Update on the WHO-NCL Network for Biologicals

programmes. The testing is performed by WHO-contracted laboratories<sup>4</sup> that are audited every 3-4 years. Currently the outcomes are reported to procurers— notably UNICEF—and manufacturers. The electronic platform will enable WHO to share this information with the Network members.

- **Regulatory lot release outcomes:** Over the past few years WHO has established 19 agreements with manufacturers, allowing a total of 10 NCLs to share their lot release data for prequalified vaccines (whether or not supplied to UN-funded programmes) with WHO. This data-sharing is part of the contract between WHO and the respective NCLs (*Box 2*). WHO is now approaching manufacturers to allow information exchange on lot release outcomes among Network members. The extent of what will be shared will depend on each individual agreement.

Some regulatory lot release information is already publicly available. For example, Swissmedic provides monthly updates on lots

released either based on its own review, or in recognition of the OCABR process.<sup>5</sup> Sharing of the responsible NCLs' lot release outcomes through the Network will support reliance initiatives in countries importing prequalified vaccines in a more systematic way.

### Benefits

The WHO Network offers some unique benefits in the global context.

### Common standards

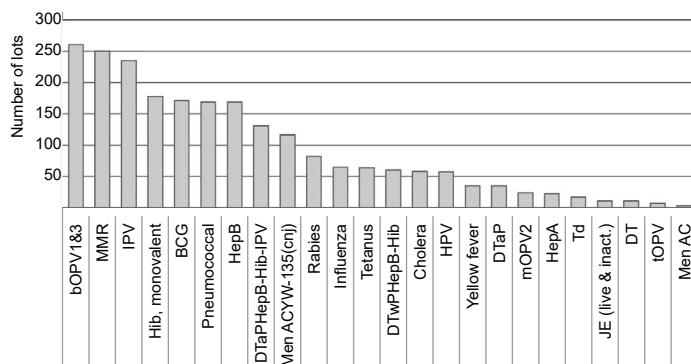
WHO is well placed to convene a global Network of partners aiming at reliance in vaccine lot release. The NRAs and NCLs found capable to oversee the quality of prequalified vaccines have all passed a comprehensive, stringent WHO assessment. In fact, the WHO indicator tool used for benchmarking regulatory systems is being refined and now also incorporates a classification system that characterizes

<sup>4</sup> See [www.who.int/immunization\\_standards/vaccine\\_quality/contracted\\_labs\\_vaccines/en/](http://www.who.int/immunization_standards/vaccine_quality/contracted_labs_vaccines/en/)

<sup>5</sup> <https://www.swissmedic.ch/swissmedic/en/home/services/laboratories--omcl-/approved-batches.html>. A specific batch number can be found through a site-specific search in the browser, e.g.: "AHBVC630A site:swissmedic.ch"

### Box 2: National lot release data reported to WHO (2016)

In 2016 ten NCLs responsible for releasing prequalified vaccines shared lot release data for a total of **2543** batches of prequalified vaccines with WHO, based on agreements with manufacturers. For comparison, 115 lots were tested on behalf of WHO.



mature regulatory authorities on whose findings WHO and others may choose to rely.<sup>6</sup>

### *Common methods and best practice*

Standardized vaccine testing methods would be a great help for manufacturers and regulators. WHO has been collaborating with Network partners to develop and implement such methods. A recent example is an assay for the Hib-component in liquid vaccine combinations,<sup>(5)</sup> which has been widely implemented. A proficiency study is under way, and the pharmacopoeial authorities of both China and India intend to incorporate the method in the next editions of their pharmacopoeias. The Network will provide a platform to encourage the adoption of harmonized methods and best practices.

In addition, some of the partners in the Network have valuable specialized expertise to offer. For example, a pilot project is under way to collaborate with Swissmedic in the framework of the authority's proteomics project that would enable "profiling" of vaccines to monitor the products circulating on the market.

### **Facilitating reliance**

While the online information-sharing platform is still under construction, the Network has already stimulated information exchange on an as-needed basis. The NCL of Bulgaria has started to share its lot release data with WHO based on a collaboration agreement.

There is considerable scope for reduction of redundant lot testing both in countries that are full and associate Network members. However, decisions are needed at national level to change the current lot

### Update on the WHO-NCL Network for Biologicals

testing policies. The example of Senegal shows that this is achievable: As a result of its Network participation, the NCL is no longer re-testing batches of imported WHO-prequalified vaccines.

### **Conclusion**

Vaccines and other biological products are essential for public health. In the era of globalization, "big data" and increased challenges faced by regulators, an in-depth understanding of processes is becoming ever more crucial to make good use of data on vaccine quality. By providing an independent global forum for information exchange, the WHO-NNB Network meets an important need.

### **References**

- 1 Wood D, Dellepiane N. Twenty-five years of the WHO vaccines prequalification programme (1987–2012): Lessons learned and future perspectives. *Vaccine* 2015;33(1):52–61. doi:10.1016/j.vaccine.2013.11.066.
- 2 WHO. *Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations Agencies*. WHO Technical Report Series 978, Annex 6. Geneva: World Health Organization, 2010.
- 3 WHO. *Guidelines for independent lot release of vaccines by regulatory authorities. Annex 2*. In: Technical Report Series No. 978. Geneva: World Health Organization; 2010.
- 4 17<sup>th</sup> International Conference of Drug Regulatory Authorities (ICDRA). Cape Town, South Africa, 29 November–2 December 2016. *Recommendations*. Workshop G: Vaccine regulation. Available at:
- 5 Roskopf U, Daas A, Terao E, von Hunolstein C. Collaborative study on saccharide quantification of the *Haemophilus influenzae* type b component in liquid vaccine presentations. *Pharmeur Bio Sci Notes* 2017(4):44-68.

<sup>6</sup> See [http://www.who.int/medicines/regulation/benchmarking\\_tool/en/](http://www.who.int/medicines/regulation/benchmarking_tool/en/).



# Medicines use

## The Prescribing Safety Assessment

**Prescribing is a complex task requiring knowledge of medicines and the diseases they are used to treat, careful judgement of risks and benefits of treatment, and attention to detail. Prescribing can improve health, but also has potential hazards. Studies have found that prescribing is the most challenging area for new graduates, and that errors are common both among trainees and professionals. The Prescribing Safety Assessment (PSA) is an online tool that allows health care professionals to develop and demonstrate their competencies in relation to the safe and effective use of medicines.**

### The importance of prescribing

Prescribing medicines is the primary tool used by all healthcare systems to treat disease, alleviate symptoms and prevent future illness. Although the majority of prescriptions are appropriate, many studies from around the world have drawn attention to the rates of prescribing errors and avoidable adverse drug reactions. In the United Kingdom (UK), errors are found in around 10% of hospital prescriptions and 5% of general practice prescriptions.<sup>(1-4)</sup> These errors matter because they not only harm patients but present unnecessary costs attributable to failed care, prolonged hospital stays and increasing litigation.

Prescribing is a high-stakes activity for all involved. For patients, medicines are a major factor affecting their health. For doctors and hospitals, prescribing represents a degree of clinical risk and significant cost. Prescribers have to select the correct medicine, dose, and route and frequency

of administration, sometimes in the face of diagnostic uncertainty, while taking into account predicted individual variability in medicine handling and response as a result of comorbidity, genetics, and interacting medicines. Newly graduated doctors write a large proportion of hospital prescriptions (medication orders), and it is therefore unsurprising that widespread evidence exists to show that prescribing by this group is frequently sub-optimum. But senior doctors also make errors, and concerns regarding prescribing skills among all prescribers have been expressed internationally.<sup>(5)</sup>

We should not be surprised that errors are made since prescribers work under very high-pressured circumstances, full of distractions. They have a heavy burden of administration and require continuous multi-tasking which results in them being more error-prone. The number, age, and vulnerability of hospital patients have

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This article was contributed by a team from the Prescribing Safety Assessment, which is delivered jointly by the [British Pharmacological Society](#) and [MSC Assessment](#). We thank Professor Simon Maxwell and Dr David James for drafting the manuscript.



## Prescribing safety assessment (PSA)

also progressively increased, as has the complexity of the treatment regimens for common disorders.

In view of this situation it might be expected that new graduates would be well prepared to begin prescribing in these demanding work environments. However, a clear theme from many studies is that students and new graduates often do not feel adequately prepared to carry out their role in prescribing, a concern echoed by their supervisors.

## Development of the PSA

### *Aim and scope*

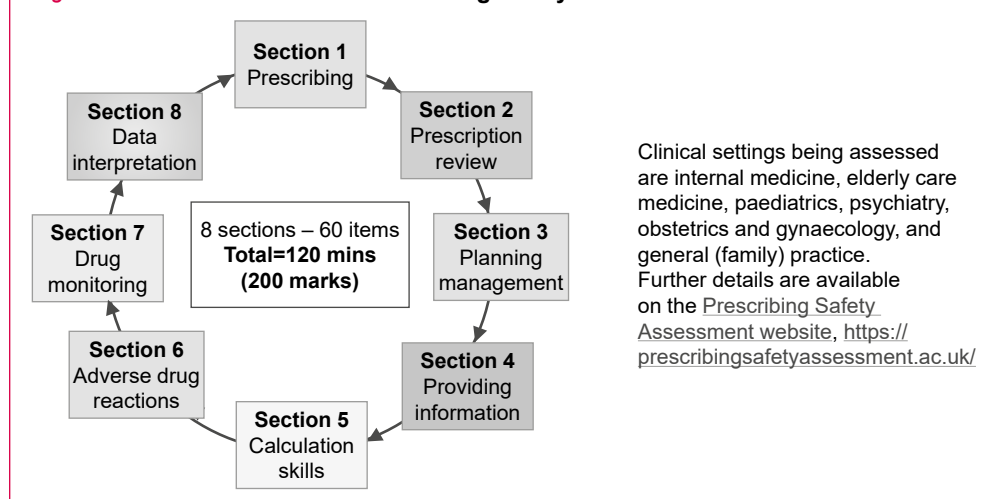
In response to this situation the British Pharmacological Society (BPS) has collaborated with the UK Medical Schools Council to develop the *Prescribing Safety Assessment (PSA)*,<sup>(6)</sup> an online training and assessment package to promote better prescribing skills in healthcare. The PSA is a valid and reliable assessment that allows final year medical students to demonstrate that they have the necessary knowledge,

skills and judgement (in relation to the safe and effective use of medicines) to begin their work as independent junior prescribers in UK hospitals. The PSA aims to bridge the gap between traditional pharmacology education and the practical application of that knowledge to patient care in the clinical environment. It presents learners with realistic clinical cases where they are scored on their performance and receive targeted feedback to improve their future performance.

### *Structure*

The PSA is based on an assessment blueprint of eight sections containing item styles that cover different aspects of the clinical activity undertaken by prescribers (*Figure 1*). The assessment is “open book” but time-limited, with candidates having access to the *British National Formulary* throughout its duration. The online nature of the assessment offers the advantage of automated marking of candidate prescriptions and provision of feedback.

**Figure 1: The structure of the Prescribing Safety Assessment**



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## Prescribing safety assessment (PSA)

### *Question items*

The PSA question items have been developed over several years by a team of around 100 trained authors (including clinical pharmacologists, other specialty and trainee doctors, general practitioners and pharmacists) who are mainly based in UK medical schools or National Health Service (NHS) hospitals. Their question items are submitted annually and undergo a strict five-stage quality assurance process overseen by the PSA Assessment Board. Items that survive each stage of review, including a national peer-review meeting, are entered into the PSA item bank, which now includes around 3 000 items. The pass marks for each paper are determined by a Standard-Setting Group comprising representatives from UK medical schools who are selected for their knowledge of the appropriate minimum standard expected of Foundation Year 1 doctors.

### *Delivery and feedback*

The PSA is delivered online from a cloud-based server located in Mumbai, India. All candidates (final year medical students) are registered on the PSA online system and sent an e-mail requesting them to activate their accounts. After activation of their accounts they have access to general information about the PSA, information videos and 1-hour, 30-item, practice papers with question-specific feedback. Candidates are encouraged to familiarize themselves with the different question types and the assessment environment and to practise finding information in the online version of the British National Formulary.

The detailed feedback associated with each question item enables the student to identify gaps in knowledge and areas for improvement. This feedback is therefore an essential tool in helping students improve

their knowledge and practice in prescribing. Formative feedback means students can take control of their own learning and allows every candidate to assess his or her own work for personal development.

The PSA can be offered formatively or summatively, and has been shown to be suitable as a standardized national prescribing assessment delivered online.<sup>(7)</sup> It is also delivered to professionals as Continuing Medical Education.

## **Growth in the PSA**

### *In the UK*

The PSA has been a huge success and has now been supported by the UK's General Medical Council and the Foundation Programme Board to the extent that all new entrants are expected to have passed it in order to continue training as a doctor in the UK, whether they come from UK medical schools or from overseas. Over 50 000 students from the UK and overseas have participated in the training and assessment, and 10 000 medical students sit the PSA each year.

A pilot study has confirmed the feasibility and acceptability of the PSA for pharmacist prescribers and benchmarked their performance against that of final year medical students.<sup>(8)</sup> For several years the PSA has been delivered to undergraduate and preregistration pharmacists from around 20 pharmacy schools in the UK. Feedback from Health Education England (HEE), students and faculty has been very positive and the number of pharmacy candidates that have taken the PSA has grown to almost 2 000.

### *Internationally*

The BPS has redeveloped the PSA platform and content to internationalize its appeal and

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**Prescribing safety assessment (PSA)**

relevance. This new version of the PSA, the *Prescribing Skills Assessment*, is delivered to medical schools in Canada, Australia, New Zealand, Malta, and Ireland and has been piloted in India, with further pilots planned for Europe, China and the Middle East.

The BPS and the Royal College of Physicians and Surgeons of Canada have been undertaking an ambitious collaboration to support safer prescribing by doctors in Canada. Representing a significant commitment by both organizations, the partnership has brought experts together to raise the profile of prescribing competency and to promote its importance through the joint development of education and assessment resources in this field. This [Prescribing Safely Canada \(PSC\)](#) initiative is intended to help physicians assess their prescribing skills, identify gaps and help correct unsafe practices and cognitive bias through a feedback loop, while providing analytics of aggregate data that can inform the Royal College of systemic gaps. This initiative is underpinned by the strategic direction of the Royal College, which is to develop a comprehensive agenda for safe prescribing of medications to support specialists that lead and develop high quality, safer care.

There is a mutual benefit for both the Royal College and the BPS to collaborate around medication safety. For the BPS, the Royal College is an attractive partner that is able to utilise the assessment and learning resources formatively as a means of professional development for more experienced clinical staff. The BPS is an equally attractive partner for the Royal College, with a robust technical platform allowing for international collaboration, educationally and psychometrically sound

assessment tools, and global expertise on the dissemination of pharmacological knowledge.

### **The future**

With the recognition it now enjoys, the PSA represents high standards of quality in medical education and training. The assessment, along with its associated training material, is greatly appreciated by students who recognize the importance of prescribing skills to their future careers. Moreover, the PSA is making a critical contribution to improved patient safety in UK healthcare.

Our future aim is to harness the experience that we have gained from a project that was originally conceived to address a concern in UK healthcare, and to use that knowledge to offer a tool that might enhance the quality of medicines usage globally. We are delighted to be counted as a stakeholder supporting WHO's [Medication Without Harm](#) theme for the third Global Patient Safety Challenge. We intend to develop, and make available, educational case-based materials that will help to embed the prescribing principles outlined in the WHO Guide to Good Prescribing,<sup>(9)</sup> largely focusing around the Essential Medicines List. To make this a reality, we would like to bring interested stakeholders together as part of an International Advisory Board.

### **References**

- 1 Elliott R, Camacho E, Campbell F, Martyn St James M, Kaltenthaler E, Wong R *et al*. Prevalence and economic burden of medication errors in the NHS in England. Rapid evidence synthesis and economic analysis of the prevalence and burden of medication error in the UK. Policy Research Unit in Economic Evaluation of Health and Care Interventions. Universities of Sheffield and York. 2018.

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**Prescribing safety assessment (PSA)**

- 2 Dornan T, Ashcroft D, Heathfield H, Lewis P, Miles J, Taylor D *et al.* An in depth investigation into causes of prescribing errors by foundation trainees in relation to their medical education: EQUIP study. Final report for the GMC, December 2009.
- 3 Ryan C, Ross S, Davey P, Duncan EM, Francis J, Fielding S *et al.* Prevalence and causes of prescribing errors: the PRescribing Outcomes for Trainee Doctors Engaged in Clinical Training (PROTECT) study. *PLoS ONE* 2014; 9(1): e79802.
- 4 Avery AJ, Ghaleb M, Barber N, Franklin B, Armstrong S, Crowe S *et al.* The prevalence and nature of prescribing and monitoring errors in English general practice: a retrospective case note review. *Br J Gen Pract.* 2013 Aug; 63(613): e543–e553.
- 5 Ross S, Bond C, Rothnie H, Thomas S, Macleod MJ *et al.* What is the scale of prescribing errors committed by junior doctors? A systematic review. *Br. J. Clin, Pharmacol.* 2009 Jun; 67(6): 629–640. Published online 16 December 2008.
- 6 Maxwell SRJ, Cameron IT, Webb DJ. Prescribing safety: ensuring that new graduates are prepared. *Lancet.* 2015;385:579–581. doi: 10.1016/S0140-6736(14)62339-4.
- 7 Maxwell SRJ, Coleman JJ, Bollington L *et al.* Prescribing Safety Assessment 2016: Delivery of a national prescribing assessment to 7343 UK final-year medical students. *Br J Clin Pharmacol.* 2017;83:2249–2258.
- 8 Reid F, Power A, Stewart D *et al.* Piloting the United Kingdom 'Prescribing Safety Assessment' with pharmacist prescribers in Scotland. *Res Social Adm Pharm.* 2018;14:62–68.
- 9 de Vries TPGM, Henning RH, Hogerzeil HV, Fresle DA. Guide to Good Prescribing. A Practical Manual. Geneva: World Health Organization Action Programme on Essential Drugs; 1994. ◊

# Safety news

## Safety warnings

### **Azithromycin:**

#### **Long term risks seen in clinical study**

Ireland, Estonia – The marketing authorization holder, in agreement with EMA and national regulatory authorities, has informed health professionals about an increased rate of relapses of haematological malignancies and mortality in haematopoietic stem cell transplantation (HSCT) patients treated experimentally with azithromycin. A clinical trial investigating the use of azithromycin to prevent bronchiolitis obliterans syndrome following HSCT was terminated early after an increased risk of relapses was seen compared with placebo. The researchers conclude that long term azithromycin exposure following HSCT may include risks which exceed the anticipated benefits.

- ▶ [HPRA Safety notice, 2 May 2018.](#)  
[Ravimiamet Safety announcement, 2 May 2018](#) (in Estonian).

### **Tosufloxacin:**

#### **Nephrogenic diabetes insipidus**

Japan – The PMDA has informed health professionals that cases of nephrogenic diabetes insipidus have been observed with the fluoroquinolone antimicrobial tosofloxacin in Japan. A warning about this adverse effect will be added to the product information.

- ▶ [PMDA Summary of investigation results and MHLW Revision of precautions, 19 April 2018.](#)

### **Dolutegravir:**

#### **Birth defects**

A study involving babies born to 11 558 HIV-positive women in Botswana— the Tsepamo Study— showed that 0.9% of babies (4 of 426) whose mothers became pregnant while taking dolutegravir had a neural tube defect, compared with 0.1% of babies (14 of 11 173) whose mothers took other HIV medicines.

European Union, Australia, United States of America – Regulatory authorities around the world have issued precautionary advice in response to the study findings. The EMA and the TGA have recommended that dolutegravir should not be prescribed to women seeking to become pregnant. Women who can become pregnant should use effective contraception while taking dolutegravir medicines.<sup>(1,2)</sup> The FDA has recommended that health professionals should exclude pregnancy before starting a dolutegravir-containing regimen in women of childbearing age, and should only prescribe the medicine to women of childbearing age if they decide that its benefits outweigh the risks. In that case, they should reinforce the need for effective contraception.<sup>(3)</sup> The regulatory authorities will continue to investigate the issue.

- ▶ <sup>(1)</sup> [EMA Press release, 18 May 2018.](#)
- ▶ <sup>(2)</sup> [TGA Safety advisory, 31 May 2018.](#)
- ▶ <sup>(3)</sup> [FDA Drug safety communication, 18 May 2018.](#)

Geneva – WHO has convened an expert guideline development group meeting and will release updated guidance on the role

of dolutegravir in first- and second-line HIV treatment in the coming months. In the interim, WHO advises countries and ministries to follow the 2016 WHO ARV Guidelines, and to consider the following:

- Pregnant women who are taking dolutegravir should not stop their ARV therapy and should speak with their health provider for additional guidance.
- Antiretroviral (ARV) therapy for women of childbearing age, including pregnant women, should be based on drugs for which adequate efficacy and safety data are available; an efavirenz-based regimen is a safe and effective first-line regimen.
- If other first-line ARVs cannot be used in women of childbearing age, dolutegravir may be considered in cases where consistent contraception can be assured.
- Programmes should continue strengthening pharmacovigilance including monitoring of birth outcomes.

The WHO Guidelines released in 2016 cautioned that there were insufficient data for using dolutegravir during pregnancy or breastfeeding and recommended efavirenz, in combination with tenofovir and lamivudine or emtricitabine, as the preferred option in pregnancy.

- ▶ [WHO. Statement on DTG – Geneva 18 May 2018.](#)

### Leaking vaccine syringes: Potential underdosing

Switzerland, Canada, Malta – GlaxoSmithKline (GSK) has provided information on syringe leaks, *i.e.* escape of fluid between the syringe and needle, that may occur with various vaccines during reconstitution or administration, resulting in a potential risk of underdosing. There are no sterility concerns, given that no leakage problems have been occurring before use.

If a leakage occurs during the reconstitution of lyophilized vaccines, the syringe should be discarded. If leakage is observed during the administration of a vaccine, the doctor must decide whether the individual concerned should be revaccinated. The potential benefit of increasing vaccination protection should be weighed against the risk of adverse events due to administration of a second full dose.

Details of the vaccines affected and further information are found in the regulatory communications referenced below.

- ▶ [Swissmedic Healthcare professional communication, 13 April 2018](#) and company information letter
- [Health Canada Advisory, 1 May 2018.](#)
- [Malta Medicines Authority. Archived Direct Healthcare Professional Communication, 9 March 2018.](#)

### Pembrolizumab, atezolizumab:

- Use restricted in EU
- Reports of sclerosing cholangitis with pembrolizumab in Japan

European Union – The EMA has restricted the use of pembrolizumab (Keytruda®) and atezolizumab (Tecentriq®) in first-line treatments for urothelial cancer. For this indication the medicines should now only be used in patients with high levels of PD-L1 protein. Early data from two clinical trials have shown reduced survival in patients with low PD-L1 levels. There is no change in the recommended use of the two medicines for second-line treatment, or for treatment of other cancers.(1)

Japan – The PMDA has informed health professionals about cases of sclerosing cholangitis reported in patients treated with pembrolizumab in Japan. Sclerosing cholangitis is characterized by swelling due to inflammation, scarring and destruction of

the bile ducts inside and outside of the liver. The product information will be updated to warn about this risk.

- ▶ (1) [EMA Press release, 1 June 2018.](#)
- ▶ (2) [PMDA Summary of investigation results and MHLW Revisions of precautions, 19 April 2018.](#)

### **Filgrastim and other G-CSFs: Aortitis**

Ireland – The marketing authorization holders, in agreement with HPRA, have informed healthcare professionals that there have been rare reports of aortitis in patients and healthy donors receiving products containing the granulocyte colony-stimulating factors (G-CSFs) filgrastim, lenograstim, lipegfilgrastim or pegfilgrastim. People receiving a G-CSF product should be instructed to seek medical attention if they develop fever, abdominal pain, malaise or back pain.(1)

The EMA's PRAC had evaluated this safety signal in February 2018 and had recommended that the product information of the G-CSF products on the European market should be updated to reflect the risk of aortitis.(2)

- ▶ (1) [HPRA Safety notice, 28 May 2018.](#)
- ▶ (2) [EMA. PRAC recommendations on signals. Adopted at the 5-8 February 2018 PRAC meeting. 22 February 2018.](#)

### **Denosumab (indicated in fractures, bone neoplasm metastasis): new malignancies**

Ireland, Estonia – The marketing authorization holder, in agreement with EMA and the national regulatory agencies, has informed health professionals of new study findings concerning denosumab (Xgeva®). New primary

malignancies were reported more frequently in clinical studies in patients with advanced malignancies treated with denosumab, compared to zoledronic acid (cumulative incidence at one year: 1.1% versus 0.6%). No treatment-related pattern in individual cancers or cancer groupings was apparent. The product information will be updated to include this information.

- ▶ [HPRA Safety notice, 17 May 2018.](#)  
[Ravimiamet \(Estonian medicines agency\). Safety announcement, 9 May 2018 \(in Estonian\).](#)

### **Lamotrigine: Rare but serious immune reaction**

United States of America – The FDA has warned that lamotrigine (Lamictal®) can cause haemophagocytic lymphohistiocytosis (HLH), a rare but very serious immune system reaction. HLH causes an uncontrolled response by the immune system and typically presents as a persistent fever. It can lead to severe problems with blood cells and organs such as the liver, kidneys, and lungs and can be fatal, especially if it is not diagnosed and treated quickly.

Lamotrigine is used to treat seizures and bipolar disorder. A new warning about this risk has been added to the product information for lamotrigine-containing medicines.

- ▶ [FDA Drug safety communication, 25 April 2018.](#)

### **Veterinary ear gel: Eye injuries in pets and owners**

European Union – The EMA has warned that an ear gel for dogs containing terbinafine, florfenicol and betamethasone acetate (Osrurnia®) has been causing eye injuries to pets or their owners after



accidental eye exposure. Care should be taken to prevent the ear gel from getting into the eyes of people or dogs. If accidental exposure occurs, the eyes should be thoroughly rinsed with water, and medical care sought. Veterinary healthcare professionals in the EU will be informed in writing of this issue.

► [EMA Press release, 20 April 2018.](#)

### Known risks

#### **Anagliptin, linagliptin, teneligliptin:** **Acute pancreatitis**

Japan – The MHLW has recommended updates to the product information for the antidiabetic medicines anagliptin, linagliptin and teneligliptin following cases of acute pancreatitis reported in patients treated with these medicines in Japan.

A warning about post-marketing reports of acute and potentially fatal pancreatitis is also found in the EMA- and FDA-approved product information for products containing linagliptin and other dipeptidyl peptidase-4 (DPP-4) inhibitors.

► [PMDA Summary of investigation results and MHLW Revisions of precautions, 20 March 2018.](#)

#### **Selexipag:** **Avoid use with CYP2C8 inhibitors**

Japan – Based on the results of a drug-drug interaction study involving selexipag (Upravi®) and gemfibrozil, a strong CYP2C8 inhibitor, the PMDA has recommended that selexipag should be contraindicated in Japan in patients receiving medicines containing clopidogrel, which is also a CYP2C8 inhibitor. Selexipag is used to treat pulmonary hypertension.

Gemfibrozil is not currently approved in Japan.

In the EU and the U.S. selexipag is contraindicated with gemfibrozil but can be used with moderate CYP2C8 inhibitors (such as clopidogrel, deferasirox or teriflunomide), although dose adjustments should be considered.

► [PMDA Summary of investigation results and MHLW Revisions of precautions, 20 March 2018.](#)

#### **Tolvaptan:** **Acute liver failure**

Japan – The PMDA has informed health professionals that cases of acute liver failure, including several fatal cases, have been reported in patients treated with tolvaptan in Japan. This medicine is used to treat hyponatraemia and – at higher doses – to slow the progression of autosomal dominant polycystic kidney disease, a rare inherited condition. The currently approved product information recommends close monitoring of liver function. The MHLW has requested that a warning about the risk of acute liver failure should be added.

Warnings about serious and potentially life-threatening liver injury are also included in the EMA- and FDA-approved product information.

► [PMDA Summary of investigation results and MHLW Revisions of precautions, 20 March 2018.](#)

#### **Oral benzocaine products:** **Rare but serious blood disorder**

United States of America – In an update to two previous communications the FDA has warned about the risk of methaemoglobinaemia associated with oral benzocaine-containing products. This is

a serious and potentially life-threatening blood disorder in which the amount of oxygen carried through the blood is greatly reduced.

The FDA has urged manufacturers to stop marketing over-the-counter oral benzocaine products for teething and mouth pain in children under two, and to include certain warnings in the product information of oral benzocaine products for adults and children aged two years and above. The FDA will take action if companies do not comply.

► [FDA Drug safety communication, 23 May 2018.](#)

## Updated recommendations

### Ulipristal

European Union – The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed its review of ulipristal acetate (Esmya®), leading to new measures to minimize the risk of rare but serious liver injury. Ulipristal is now contraindicated in women with known liver problems. New treatment courses may be started only if patients are tested and have liver enzyme levels at most 2 times the upper limit of normal. Tests should be repeated once a month during the first two treatment courses and two to four weeks after stopping treatment. If liver enzyme levels rise above 3 times the upper limit of normal, treatment should be stopped and the patient closely monitored. Ulipristal should be used for more than one treatment course only in women who are not eligible for surgery. A card will be included with the medicine to inform women about the need for liver monitoring and for seeking medical help in case of suspected liver problems.

Ulipristal is used to treat moderate to severe symptoms of uterine fibroids. The review was triggered in November 2017 by reports of serious liver injury. In February 2018 the PRAC had issued interim recommendations against starting ulipristal in new patients.

► [EMA Press release, 1 June 2018.](#)

### Antimicrobials

#### Japan aligns product information

Japan – The PMDA has recommended that the product information for 164 antimicrobial medicines approved in Japan be updated in line with the national *Guidance for Appropriate Use of Antimicrobials*. This guidance focuses on the appropriate treatment of patients with acute respiratory tract infections and those with acute diarrhoea. Based on data from Japan and other countries, these two patient groups are believed to be subjected to particularly frequent and unnecessary antimicrobial treatment. The affected medicines are indicated for the treatment of pharyngitis/laryngitis, tonsillitis, acute bronchitis, infectious enteritis or sinusitis.<sup>(1)</sup>

In other moves to align the product information in Japan with that approved elsewhere, the Agency has recommended that adrenaline can be used for emergency treatment of anaphylaxis in patients receiving alpha blockers, despite the risk of decreased blood pressure induced by adrenaline reversal,<sup>(2)</sup> and propofol can be given to pregnant women, or women who may be pregnant, provided that the potential

benefits outweigh the risk of neonatal respiratory depression.<sup>(3)</sup>

- ▶ <sup>(1)</sup> [PMDA Report on investigation results, 7 March 2018, and MHLW Revisions of precautions, 27 March 2018.](#)
- <sup>(2)</sup> [PMDA Report on investigation results, 2 March 2018.](#)
- <sup>(3)</sup> [PMDA Report on investigation results, 1 March 2018, and MHLW Revision of precautions, 27 March 2018.](#)

### Dengue vaccine

Geneva – WHO's Strategic Advisory Group of Experts on Immunization (SAGE) has published its revised recommendations on the use of the dengue vaccine CYD-TDV (Dengvaxia®). Results from additional safety studies conducted by the manufacturer had shown that the vaccine is associated with an increased risk of severe dengue in seronegative individuals, starting about 30 months after the first dose.

The SAGE weighed two strategies for achieving high population protection from dengue: consideration of population seroprevalence criteria, and pre-vaccination screening. Acknowledging that both are programmatically difficult, the SAGE expressed its preference for screening and vaccinating only dengue-seropositive persons.

Screening can be done using the dengue IgG ELISA, interpreted in a local context depending on the prevalence of other flaviviruses and past use of flavivirus vaccines (such as Japanese encephalitis and yellow fever vaccines), or—in high transmission settings—rapid tests, although these have a lower sensitivity and specificity than serological testing. Decisions about implementing pre-vaccination screening will require careful assessment of the sensitivity and specificity of available tests, local

priorities, dengue epidemiology, country-specific dengue hospitalization rates, and affordability of both CYD-TDV and screening tests in each country.

Going forward there is a need to develop a highly sensitive and specific rapid diagnostic test, and to simplify immunization schedules.

- ▶ [WHO. Revised SAGE recommendation on use of dengue vaccine. 19 April 2018.](#)

### Daclizumab: Risk outweigh benefits

European Union – The EMA has confirmed that the multiple sclerosis medicine daclizumab beta (Zinbryta®) poses a risk of serious and potentially fatal immune reactions affecting the brain, liver and other organs. The marketing authorization in the EU was voluntarily withdrawn by the company in March 2018. Healthcare professionals should continue monitoring patients who have been treated with daclizumab in line with recommendations issued in March 2018.<sup>(1)</sup>

Australia – The TGA has informed health professionals that the marketing authorization holder is coordinating a worldwide withdrawal of daclizumab. To give time for patients to transition off the medicine it will be supplied in Australia until 31 May 2018. <sup>(1)</sup>

- ▶ <sup>(1)</sup> [EMA Press release, 18 March 2018.](#)
- <sup>(2)</sup> [TGA Alert, 15 March 2018.](#)

**Other updates****Hydroxyethyl starch:  
Suspension maintained**

European Union – Following the recommendation by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) in January 2018 to suspend the marketing authorizations for hydroxyethyl starch solutions for infusion across the EU, the European Commission had requested the Committee to further consider any possible unmet medical need that could result from the suspension, as well as the feasibility and likely effectiveness of additional risk minimization measures.<sup>(1)</sup> At its meeting held in May 2018 the PRAC maintained its recommendation. In line with regulatory procedure this recommendation was then sent to the Coordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh) of the European Heads of Medicines Agencies (HMA) network for its consideration.<sup>(2)</sup>

- ▶ <sup>(1)</sup> [EMA News, 13 April 2018.](#)
- ▶ <sup>(2)</sup> [EMA News, 18 May 2018.](#)

**Quinolones and fluoroquinolones:  
Public hearing**

European Union – Quinolone and fluoroquinolone antibiotics are under review by the PRAC due to the risk of persistent serious side effects mainly affecting muscles, joints and the nervous system. In response to significant public interest, a public hearing was scheduled for 13 June 2018.<sup>(1)</sup> The EMA received 115 applications to attend, including 55 requests to speak and 60 to participate as observers. Of the former, 23 speakers from 11 EU Member States were selected to share their views directly with the PRAC; the other 22 will provide written contributions that will be considered by the scientific committee and published on the EMA website.<sup>(2)</sup>

This is the second public hearing during an EMA safety review of a medicine. The first one was held in September 2017 to inform the review of valproate, leading to additional measures to avoid its use in pregnancy.

- ▶ <sup>(1)</sup> [EMA Press release, 9 April 2018.](#)
- ▶ <sup>(2)</sup> [EMA Press release, 7 June 2018.](#)

## Reviews started

Medicine	Use	Concerns	Reference
<b>Omega-3 fatty acid medicines</b>	Prevention of recurring heart disease or stroke	An analysis of 10 studies in around 78 000 patients has found that adding omega 3-fatty acid medicines to standard treatment did not significantly reduce heart attacks, stroke or other heart and circulatory problems. These findings were similar to those from 2012 studies.	▶ <a href="#">EMA. Start of Article 31 referral.</a> 22 March 2018.
<b>Ulipristal acetate</b> (Fibristal®)	Treatment of uterine fibroids	Canadian and European reports of serious adverse events affecting the liver. The EMA has recommended new measures to minimize the risk (see page 203).	▶ <a href="#">Health Canada Advisory.</a> 15 March 2018.
<b>Methotrexate</b>	Treatment of inflammatory diseases, such as arthritis and psoriasis; treatment of certain cancers	Dosing errors, causing continued reports of serious adverse events, including fatalities. Methotrexate is used in higher doses and frequency to treat cancer than to treat inflammatory diseases.	▶ <a href="#">EMA Press release, 13 April 2018.</a>
<b>Metamizole</b> (also known as dipyron)	Treatment of severe pain and fever that cannot be controlled with other treatments	Substantial differences between EU member states in recommended maximum daily doses and contraindications during pregnancy or in women who are breastfeeding.	▶ <a href="#">EMA begins review of medicines containing metamizole.</a> 1 June 2018.
<b>Curcumin-containing supplements</b> (The warning does not apply to turmeric used in food)	Dietary supplements for joint, digestive and cardiovascular support	Potential interaction with warfarin that could lead to an increased risk of bleeding. A marked INR increase was reported in a patient on warfarin in New Zealand after starting curcumin supplements.	▶ <a href="#">Medsafe Monitoring communication.</a> 17 April 2018.

## Falsified medicines

### Falsified hepatitis B vaccines circulating in Uganda

The **WHO Medical Product Alert No. 3/2018** relates to falsified versions of multi-dose (10ml) hepatitis B vaccines (rDNA) that have been identified in Uganda.

WHO was informed by the Uganda National Drug Authority (NDA) that this falsified vaccine was available at patient level in a number of locations in the Central, South-Western and Eastern regions of Uganda. Investigations are ongoing, and samples are being collected for full laboratory analysis. The source of the falsified product has not yet been identified.

The genuine product is manufactured by the Serum Institute of India Pvt Ltd and is WHO-prequalified. Falsified versions of 10 different batch numbers have so far been discovered (see below). Based on label inconsistencies the Serum Institute of India has confirmed that the products with these details are falsified.

No adverse reactions have been reported to WHO at this stage.

**Product name:** Multi dose (10ml) Hepatitis B Vaccines (rDNA)

**False manufacturer name stated on the label:** Serum Institute of India

Batch number	Manufacturing date	Expiry Date
035L6010	MAY 2016	APR. 2019
035L5010	(None indicated)	SEP. 2019
035L006	MAR. 2016	FEB. 2020
035L3004	MAY 2015	SEPT. 2018
035L5012	(None indicated)	OCT. 2018
035L7037	10/2017	09/2020
035L6005	(None indicated)	09/2019
035L5013	11/2017	01/2020
035L5017	(None indicated)	Oct 2019
035L5007	(None indicated)	07/2018

► [WHO Medical Product Alert No. 3/2018, 23 March 2018.](#)

[PDF version \(includes photographs\)](#)

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

# Regulatory news

## Guidance

### EU: Good pharmacogenomic practice

European Union – The EMA has released its new *Guideline on good pharmacogenomic practice*, which will come into effect on 1 September 2018. The guideline describes requirements for choosing appropriate genomic methodologies during the development and the life cycle of a medicine. It discusses the characteristics of a robust clinical genomic dataset and highlights the key scientific and technological aspects to consider when determining and interpreting genomic biomarker data and translating them into clinical practice. The guideline is also expected to be a useful reference in the context of future legislation on companion diagnostics, in-house testing and medical devices in Europe.

- ▶ EMA Committee for Medicinal Products for Human Use (CHMP). [Good pharmacogenomic practice](#). 22 February 2018.

### U.S.: Genomic-based tests

United States of America – The FDA has finalized two guidance texts to drive the design, development and validation of *in vitro* diagnostics (IVDs) that use next generation sequencing (NGS) technologies. These diagnostics can look at millions of DNA changes in a single test, and have led to the identification of many new genetic variants. The first guidance relates to the use of FDA-recognized databases to support the clinical validation of new NGS tests, enabling developers to identify an efficient

path for marketing clearance or approval of their products.<sup>(1)</sup> The second guidance provides recommendations for designing, developing, and validating NGS-based tests intended to aid clinicians in the diagnosis of symptomatic individuals with suspected germline diseases. It does not address tests intended for use in the sequencing of healthy individuals.<sup>(2)</sup>

- ▶ FDA News release, 12 April 2018.

<sup>(1)</sup> FDA. [Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based \*In Vitro\* Diagnostics](#). 13 April 2018.

<sup>(2)</sup> FDA. [Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing \(NGS\) – Based \*In Vitro\* Diagnostics \(IVDs\) Intended to Aid in the Diagnosis of Suspected Germline Diseases](#). 13 April 2018.

### UK: Data integrity

United Kingdom – The MHRA has published its final guidance on data governance systems across all good practice sectors, including good laboratory practice, good clinical practice, good manufacturing practice, good distribution practice and good pharmacovigilance practice. This new guidance was created in response to fundamental failures identified by MHRA and international regulatory partners during inspections, many of which have resulted in regulatory action. It addresses the new technologies used to generate regulatory data—for example electronic data capture, automation of systems and use of remote technologies—and the increased complexity



of supply chains and ways of working, for example via third party service providers.

- ▶ [MHRA News, 9 April 2018.](#)  
MHRA. 'GXP' Data Integrity Guidance and Definitions. Revision 1: March 2018.

## Pre-market assessment

### Australia: New regulatory pathways

Australia – The TGA has established two new pre-market pathways for medicines, following recommendations of the national medicines and medical devices regulation review.

Firstly, a new provisional approval pathway for prescription *medicines* has been introduced. Approval through this pathway is on the basis of preliminary clinical data and is limited to six years. The pathway applies to new medicines as well as new uses for existing medicines. To be eligible, a product must target a serious condition, compare favourably with existing medical products and offer a major therapeutic advance. Furthermore there must be evidence of a plan to submit comprehensive clinical data.<sup>(1)</sup> In April 2018, olaratumab(rmc) (Lartruvo<sup>®</sup>) was the first medicine to be accepted for evaluation through this pathway.<sup>(2)</sup>

Secondly, the TGA has published its *Assessed listed medicines evidence guidelines*, along with guidance for completing applications. This new route sits between the pathways for “listed medicines” (complementary medicines with low risk) and “registered medicines” (fully reviewed products with higher risk). Assessed listed medicines can only contain certain defined low-risk ingredients but are used for at least one “intermediate level indication” requiring some proof of efficacy. Applicants must submit scientific evidence of the product’s efficacy to the TGA for

assessment, whereas they can self-certify the quality and safety of the product.<sup>(3)</sup>

These initiatives are part of a series of reforms undertaken in response to the regulatory review. Another new pathway for medicines—priority review—came into effect on 1 July 2017, and the first medicine, alectinib (Alecensa<sup>®</sup>) was registered via this route in February 2018.<sup>(4)</sup> An expedited approval pathway for needed novel medical devices started in 2018.<sup>(5)</sup> An overview of changes delivered and upcoming reforms in response to the medicines and medical devices regulation review is available on the TGA website.<sup>(6)</sup>

- ▶ <sup>(1)</sup> [TGA News, 20 March 2018.](#)
- <sup>(2)</sup> [TGA News, 16 April 2018.](#)
- <sup>(3)</sup> [TGA. Assessed listed medicines pathway for complementary medicines. 27 March 2018.](#)
- <sup>(4)</sup> [TGA News, 6 February 2018.](#)
- <sup>(5)</sup> [Priority review designations medical devices \(including IVDs\). 13 February 2018.](#)
- <sup>(6)</sup> [TGA. Medicines and medical devices regulation review \[webpage\]. Updated 20 March 2018. https://www.tga.gov.au/mmdr](#)

### EU: Two years of PRIME Scheme

European Union – The EMA has published a report looking back on two years’ experience with the its PRIME (PRiority Medicines) Scheme, which aims to support and optimize product development for unmet medical needs. Of 177 medicines submitted 36 have been accepted as eligible to the scheme, including 30 intended to treat rare diseases and 16 intended to treat children. The EMA has provided scientific advice for 22 of the 36 medicines, often with input from health technology assessment bodies that make recommendations on financing or reimbursement of medicines in national healthcare systems.

- ▶ [EMA News, 7 May 2018.](#)

## Medical devices

### IMDRF meeting held

Shanghai, China – The International Medical Device Regulators Forum (IMDRF) held its 13<sup>th</sup> management committee meeting in Shanghai, China, on 20–22 March 2018. The IMDRF is currently working on a unique device identification (UDI) application guide, personalized medical devices, standards for improving the quality of international medical device standards for regulatory use, adverse event terminology, good regulatory review practices, patient registries and regulated product submission. Clinical evaluation of medical devices was adopted as a new work item.

At a one-day open stakeholder forum held on the second meeting day some 500 participants discussed issues of current interest, particularly the use of artificial intelligence in the field of medical devices.

The IMDRF management committee is composed of regulatory representatives of the IMDRF members, *i.e.* Australia, Brazil, Canada, China, Europe, Japan, Russia, Singapore, South Korea, and the United States of America. WHO and the Regulatory Harmonization Steering Committee of APEC's Life Sciences Innovation Forum are IMDRF observers. The next committee meeting will be held in Beijing, China, on 18–20 September 2018.

► [CFDA News, 23 March 2018](#).  
[IMDRF Meetings \[webpage\]](#).

### Canada: Disinfectants and sterilants reclassified

Canada – Health Canada has announced a reclassification of high-level disinfectant and sterilant solutions (as defined by the Agency on its website) intended for use on medical devices. Only those products that meet the

definition of an antimicrobial agent will continue to be regulated under the Food and Drug Regulations; the others will be subject to the requirements of the Medical Devices Regulations (MDR).

The reclassification is part of Health Canada's initiatives to align its regulatory requirements with those of the United States. Manufacturers of non-antimicrobial disinfectants and sterilants licensed as medicines have a transition period of 18 months to apply for Class II medical device licences. Health Canada intends to pursue an amendment to the MDR that would reclassify these products under the higher risk Class III category.

► [Health Canada Notice, 16 March 2018](#).

## Databases

### Japan: Medicines use in children

Japan – The PMDA has provided an update on the use of its Pediatric Medical Data Collecting System, which was established in 2012 for the collection and analysis of data on the safe use of medicines in children. The system utilizes a large network of institutions and has accumulated electronic medical records of approximately 250 000 patients.

A project started in 2017 to organize and analyse these data alongside information from the literature and from other regulatory authorities. A preliminary analysis focusing on four selected medicines has now been completed. The diuretics spironolactone and furosemide were found to be frequently co-prescribed, and although the package insert states only a dosage for adults they were often used in children as well. The antiepileptic levetiracetam has a dosage specified for children from age four, but was found to be given to younger children too; a clinical investigation of its

use in these children is under way. Aspirin is indicated for Kawasaki disease, a rare condition which affects mainly children under five and is more common in Japan than in other parts of the world. Only 20% of the cases in the database had a diagnosis of Kawasaki disease; about a third of the remaining ones had a diagnosis related to thrombosis.

The analysis will be expanded and refined by inclusion of body weight data, more intensive collection of data on prescribed doses, and extraction of adverse event data.

- ▶ [PMDA. Pharmaceuticals and Medical Devices Safety Information No. 353. May 2018:3-7.](#)

### U.S.: Mobile app launched

United States of America – The FDA has announced the availability of its Drugs@FDA Express mobile application.

The new mobile app is a streamlined version of the Agency's [Drugs@FDA webpage](#). It allows users to search on their mobile devices for certain information on FDA-approved medicines based on product name, active ingredient or application number using a single search box. The app will also display the most recent product approvals within seven days, and a number of useful links and contact information.

- ▶ [FDA In Brief. 22 March 2018.](#)

## Collaboration

### Treaty for African Medicines Agency signed

Geneva – The ministers of health of African Union member states have unanimously adopted the Treaty for the establishment of the African Medicines Agency (AMA). This Agency will promote the harmonization of policies, standards and guidelines for

medical products regulation and advocate for the use of the [AU Model Law on Medical Products Regulation](#). The AMA will provide a common framework for regulatory actions, with centres of regulatory excellence that can give guidance and technical assistance to countries that lack regulatory capacity and resources. The Treaty is to be sent to the African Union's Specialised Technical Committee on Justice and Legal Affairs later in 2018.<sup>(1)</sup>

The AMA is modelled on the setup of the EMA, a unique regulatory network of national competent authorities in the Member States of the European Economic Area (EEA) working together with the EMA and the European Commission. The future AMA builds on the successes of long-standing efforts for regulatory strengthening, through the WHO-supported [African Medicines Regulatory Harmonisation \(AMRH\) Programme](#), and through the [African Vaccine Regulatory Forum \(AVAREF\)](#), which was instrumental in coordinating clinical trials for an Ebola vaccine and could be transitioned into a centre for assessment of multi-country clinical trials for a wide range of new medicines and medical devices. These achievements will greatly help the formidable task of setting up a regulatory network among 54 African member states serving a total population of over 1 billion people.<sup>(2)</sup>

- ▶ <sup>(1)</sup> [African Union Press release, 20 May 2018.](#)
- <sup>(2)</sup> [Intellectual Property Watch. Enter The African Medicines Agency, Continent's First Super-Regulator? 3 July 2017.](#)

### API inspection programme

The partners in the International Active Pharmaceutical Ingredient (API) Inspection Programme have published their report

on activities in 2011–16. In that period, they conducted 1333 GMP inspections in 20 countries outside their own territories. Between them, the partners inspected a total of 458 sites of common interest, of which 226 (49%) were located in India, and 165 (36%) in China. Non-compliances were found at 28% of all sites. Of the 1333 inspections, 131 were conducted by the WHO Prequalification Team.

The collaboration started as a pilot in 2008 and became a full programme in January 2011. It allows the EMA, national regulators of five European countries, the U.S. FDA, Australia's TGA, Health Canada and Japan's MHLW and PMDA, as well as the European Directorate for the Quality of Medicines (EDQM) and WHO, to share information on inspections of foreign API manufacturing sites. Since 2011 the membership, the number of sites of common interest, the level of information shared, and overall inspection coverage have all increased. The partners will now seek ways to improve their electronic information exchange platforms and programme reviews further.

- ▶ [EMA News, 12 April 2018.](#)  
[Report on the International Active Pharmaceutical Ingredient Inspection Programme 2011 – 2016.](#) March 2018.

### **PIC/S updates**

Geneva – The Pharmaceutical Inspection Co-operation Scheme (PIC/S) held meetings of its Committee and Executive Bureau in Geneva on 16–18 April 2018. The PIC/S Committee adopted a new PIC/S guidance on reliance in GMP inspections of foreign manufacturing sites and revised Chapters 3, 5 and 8 of the PIC/S GMP guide, to enter into force on 1 July 2018. From the same

date PIC/S will also adopt the EU guidelines on GMP excipient risk assessment, exposure limits and good distribution practices for active pharmaceutical ingredients. Furthermore, the Committee has adopted an aide-memoire on cross-contamination in shared facilities. A revised draft guidance on data integrity will be implemented for a trial period while being published for external consultation.

- ▶ [PIC/S Press release, May 2018.](#)

### **9<sup>th</sup> Meeting of World Pharmacopoeias**

Hanoi, Viet Nam – Thirteen national, regional and international pharmacopoeias representing 50 pharmacopoeial authorities around the world gathered in Da Nang, Viet Nam on 18–19 April 2018 to attend the 9<sup>th</sup> International Meeting of World Pharmacopoeias (IMWP). This event has been convened by WHO since 2012, with the first eight meetings focusing on the development of good pharmacopoeial practices. The 2018 meeting focused on creating new collaboration models and improving information-sharing. The participants agreed to establish a pharmacopoeial alert system to exchange information on issues detected with products covered by monographs that necessitate urgent action by a pharmacopoeia. The delegations also agreed to use the annual IMWP as a discussion forum to inform each other of recent challenges and to share solutions.

The 10<sup>th</sup> International Meeting of World Pharmacopoeias meeting will be held in New Delhi, India, in February 2019.

- ▶ [WHO Representative Office, Viet Nam.](#)  
[International meeting of world pharmacopoeias says collaboration is key to improving access to essential medicines.](#) 11 May 2018.

## Under discussion

European Union – The European Medicines Agency (EMA) has released a draft revised guideline on the **clinical evaluation of vaccines**. The proposed revision addresses advances in science and technology and adds considerations on priming and boosting strategies and on developing vaccines for emerging pathogens for which it might be problematic to conduct clinical trials outside of outbreaks.

► [EMA News, 26 April 2018](#).

Closing date: 30 October 2018.

European Union – The European Commission has proposed a set of recommendations on strengthening **EU cooperation to fight vaccine-preventable diseases**. The proposal comes as recent data point to vaccination gaps in Europe, for example with regard to measles and influenza.

► [European Commission Press release, 26 April 2018](#).

The Commission's proposal will be discussed by the European Council, with the aim of seeing a Council recommendation adopted before the end of 2018, with an immediate entry into force.

Canada – The government of Canada has published its proposed **pathogens of interest list** for public comment. The list largely adopts the *Global Priority List of Antibiotic-Resistant Bacteria* issued by WHO in 2017. It names the bacterial pathogens that may cause serious, life-threatening infections in the Canadian population and for which new therapies need to be developed.

► [Government of Canada. Notice, 17 April 2018](#).

Closing date: 1 July 2018.

United States of America – The FDA has released a draft guidance documents on **postmarketing safety reporting requirements for combination products**, *i.e.* products composed of two or more different types of medical products (medicine, medical device and/or biological product). In addition, the Agency has published an immediately-in-effect guidance titled *Compliance Policy for Combination Product Postmarketing Safety Reporting*.

► [FDA. Postmarketing Safety Reporting for Combination Products \[webpage\]](#).

[FDA Federal Register Notice, 21 March 2018](#).

Closing date: 19 June 2018.

Australia – The TGA has published a proposal that would require medicine sponsors to **report all medicines shortages** in confidence to the TGA. Shortages classified under a revised protocol as of “extreme” or “high” patient impact would be mandatorily published via the Medicines Shortages Information Initiative on the TGA website.

► [TGA Consultation, 27 March 2018](#).

Closing date: 30 April 2018.

European Union – The European Commission (EC) is seeking comments on a one-health approach to **counteracting the threat from infectious diseases**. The roadmap document proposes a strategy with three pillars to protect European citizens from emerging and highly pathogenic agents.

► [EC Initiative, 26 March 2018](#).

Closing date: 23 April 2018.

## Approved

### Fostamatinib for thrombocytopenia

**Product name:** Tavalisse®

**Dosage form:** Tablets

**Class:** Tyrosine kinase inhibitor;

*ATC code (temporary):* B02BX09

**Approval:** FDA

**Use:** Treatment of adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

**Benefits:** Ability to achieve a stable platelet count to reduce the risk of bleeding.

**Safety information:** The main adverse effects include hypertension, liver toxicity, diarrhoea and neutropenia. Fostamatinib can cause foetal harm.

► [FDA Prescribing information for Tavalisse®](#).  
Revised: 04/2018

### Avatrombopag to treat thrombocytopenia before procedures in certain patients

**Product name:** Doptelet®

**Dosage form:** Tablets

**Class:** Thrombopoietin receptor agonist;

*ATC code:* B02BX05

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

**Use:** Treatment of thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a medical or dental procedure

**Benefits:** Ability to increase platelet count, reducing the need for platelet transfusion or rescue therapy.

**Safety information:** Medicines of this class have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease.

► [FDA News release, 21 May 2018](#).

### Tildrakizumab for psoriasis

**Non-proprietary name in the U.S.:**

Tildrakizumab-asmn

**Product name:** Ilumya®

**Dosage form:** Injection

**Class:** Interleukin-23 antagonist;

*ATC code:* L04AC17

**Approval:** FDA

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

**Benefits:** Significant clinical improvement in skin clearance compared to placebo.

**Safety information:** Tildrakizumab may increase the risk of infections. The medicine should not be administered to patients with active tuberculosis.

► [FDA. Prescribing information for Ilumya®](#).  
Revised: 03/2018.

### Erenumab for prevention of migraine

**Non-proprietary name in the U.S.:** Erenumab-aooe

**Product name:** Aimovig®

**Dosage form:** Subcutaneous injection for once-monthly self-administration

**Class:** Calcitonin gene-related peptide receptor antagonist (first-in-class); *ATC code:* N02CX07

**Approval:** FDA; EMA

**Use:** Preventive treatment of migraine in adults. In the EU the medicine is indicated only in adults who have at least 4 migraine days per month.

**Benefits:** More effective than placebo in reducing the number of days with migraine.

► [FDA News release, 17 May 2018](#).  
[EMA Press release, 1 June 2018](#).

### Lofexidine for opioid use disorder

**Product name:** Lucemyra®

**Dosage form:** Tablets

**Class:** Central alpha-2 adrenergic agonist;

*ATC code:* N07BC04

**Approval:** FDA (priority review, fast track designation)

**Use:** Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation

Approved

in adults. The product is only approved for treatment for up to 14 days.

**Benefits:** Reduces the release of norepinephrine, the actions of which in the autonomic nervous system are believed to play a role in many of the symptoms of opioid withdrawal.

**Safety information:** The main risks include hypotension, bradycardia, and syncope, QT prolongation, and an increased risk of opioid overdose after opioid discontinuation. Safety and efficacy have not been established in people under 17 years of age.

**Note:** This is the first FDA-approved non-opioid treatment for the management of opioid withdrawal symptoms.

► [FDA News release, 16 May 2018.](#)

### Pegvaliase for phenylketonuria

**Product name:** Palynziq®

**Non-proprietary name in the U.S.:** Pegvaliase-pqpz

**Dosage form:** Injection for subcutaneous use

**Class:** Phenylalanine-metabolizing enzyme

**Approval:** FDA

**Use:** Treatment of adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management.

**Benefits:** Ability to reduce blood phenylalanine concentrations.

**Safety information:** Risk of anaphylaxis, especially during upward titration of the dose within the first year of treatment.

► [FDA News release, 24 May 2018.](#)

### Inotersen for a rare hereditary deficiency

**Product name:** Tegsedi®

**Dosage form:** Solution for injection

**Class:** Antisense oligonucleotide

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

**Use:** Treatment of stage 1 or stage 2 polyneuropathy in patients with hereditary transthyretin amyloidosis (hATTR). Efficacy in stage 3 polyneuropathy has not yet been demonstrated.

**Benefits:** Clinically relevant effects on the neurological manifestations of hATTR and on patients' quality of life.

**Notes:** hATTR is diagnosed in about three of every 10 million people in Europe every year. Current therapeutic options are liver transplant, treatment with the nervous system medicine tafamidis, and off-label use of a non-steroidal anti-inflammatory drug.

► [EMA Press release, 1 June 2018.](#)

### New formulation

#### Fosnetupitant and palonosetron injection

**Product name:** Akynzeo®

**Newly approved dosage form:** Intravenous injection

**Approval:** FDA

**Use:** Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy.

**Note:** An oral fixed-dose combination of palonosetron and netupitant was approved by the FDA in 2014.

► [FDA Product information for Akynzeo®, revised 04/2018.](#)

### Extensions of indications

#### Brentuximab vedotin for Hodgkin lymphoma

**Product name:** Adcetris®

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

**Newly approved use:** Treatment of adult patients with previously untreated stage III or IV classical Hodgkin lymphoma, in combination with chemotherapy.

**Safety information:** The product carries a boxed warning highlighting the risk of John Cunningham virus infection resulting in progressive multifocal leukoencephalopathy. Serious risks include peripheral neuropathy; severe allergic (anaphylaxis) or infusion-site



## Approved

reactions; damage to the blood, lungs and liver; serious or opportunistic infections; metabolic abnormalities (tumour lysis syndrome); serious dermatologic reactions and gastrointestinal complications. The medicine can cause harm to a developing foetus.

- ▶ [FDA News release, 20 March 2018.](#)

### Blinatumomab for acute lymphoblastic leukaemia

**Product name:** Blincyto®

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

**Newly approved use:** Treatment of adults and children with B-cell precursor acute lymphoblastic leukaemia (ALL) who are in remission but have minimal residual disease.

**Safety information:** The medicine carries a boxed warning about cytokine release syndrome and neurological toxicities observed in some clinical trial participants at the start of the first treatment. Serious risks include infections, effects on the ability to drive and use machines, pancreatitis, and adverse events caused by preparation or administration errors. There is a risk of serious adverse reactions in children due to benzyl alcohol preservative; therefore, the drug prepared with preservative-free saline should be used for patients weighing less than 22 kg.

- ▶ [FDA News release, 29 March 2018.](#)

### Dabrafenib with trametinib for certain thyroid cancers

**Product name:** Tafinlar® in combination with Mekinist®

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

**Newly approved use:** Treatment of locally advanced or metastatic anaplastic thyroid cancer with BRAF V600E mutation

**Note:** This is the first FDA-approved treatment for patients with this aggressive form of thyroid cancer.

- ▶ [FDA News release, 4 May 2018.](#)

### Fingolimod for multiple sclerosis in children

**Product name:** Gilenya®

**Approval:** FDA (priority review, break-through therapy)

**Newly approved use:** Treatment of relapsing multiple sclerosis in children and adolescents aged 10 years and older.

**Safety information:** Fingolimod can cause slowing of the heart rate, especially after the first dose; serious infections, including progressive multifocal leukoencephalopathy (PML); and a number of other adverse effects. Patients should be monitored for infection during treatment and for two months thereafter.

- ▶ [FDA News release, 11 May 2018.](#)

### Tofacitinib for ulcerative colitis

**Product name:** Xeljanz®

**Approval:** FDA

**Newly approved use:** Treatment of adults with moderately to severely active ulcerative colitis

**Safety information:** Increased risk of developing serious infections that may lead to hospitalization or death; as well as lymphoma and other malignancies, have been observed in patients treated with tofacitinib.

**Notes:** Tofacitinib is the first FDA-approved oral medicine for chronic use in ulcerative colitis.

- ▶ [FDA News release, 30 May 2018.](#)

## Biosimilars

### Epoetin alfa

**Non-proprietary name in the U.S.:**

Epoetin alfa-epbx

**Product name:** Retacrit®

**Use:** Treatment of anaemia caused by chronic kidney disease, chemotherapy, or use of zidovudine in patients with HIV infection; reduction of allogeneic red blood cell transfusions in patients undergoing elective, non-cardiac, non-vascular surgery.

- ▶ [FDA News release, 15 May 2018.](#)

Approved

## Trastuzumab

**Product name:** Kanjinti®

**Use:** Treatment of metastatic breast cancer, early breast cancer, and metastatic gastric cancer.

► [EMA Summary of opinion, 22 March 2018.](#)

**Product name:** Trazimera®

**Use:** Treatment of metastatic breast cancer, early breast cancer, and metastatic gastric cancer.

► [EMA Summary of opinion, 31 May 2018.](#)

## Pegfilgrastim

**Non-proprietary name in the U.S.:**

Pegfilgrastim-jmdb

**Product name:** Fulphila®

**Use:** To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

► [FDA News release, 4 June 2018.](#)

## Infliximab

**Product name:** Zessly®

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

► [EMA Summary of opinion, 22 March 2018.](#)

## Adalimumab

**Product name:** Halimatoz®

**Use:** Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque

psoriasis, hidradenitis suppurativa, uveitis and paediatric uveitis.

► [EMA Summary of opinion, 31 May 2018.](#)

**Product name:** Hefiya®

**Use:** Treatment of juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, uveitis and paediatric uveitis.

► [EMA Summary of opinion, 31 May 2018.](#)

**Product name:** Hyrimoz®

**Use:** Treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, paediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, paediatric Crohn's disease, ulcerative colitis, uveitis and paediatric uveitis.

► [EMA Summary of opinion, 31 May 2018.](#)

## Diagnostics

### Mass spectroscopy test for *Candida auris*

United States of America – The FDA has authorized the first test to identify *Candida auris*, an emerging pathogen which can cause serious infections in hospitalized patients and is frequently resistant to multiple antifungal drugs. The approval permits a new use for a mass spectrometry-based diagnostic system that has previously been authorized by the FDA to identify a wide range of pathogen species.

The FDA plans to propose exempting certain mass spectrometry microorganism identification system processes from an additional premarket review once they have achieved initial FDA authorization. This would permit easy updates to device-specific organism databases to expand the capabilities of these devices.

► [FDA News release, 20 April 2018.](#)

## Negative opinions

Three medicines approved in the U.S. have received negative opinions in the European Union. In all three cases the applicants have requested a re-examination of the negative EMA opinion.

### Betrixaban

**Product name:** Dexxience®

**Dosage form:** Capsules

**Class:** Anticoagulant, Factor Xa inhibitor

**Regulatory authority:** EMA

**Intended use:** Prevention of venous thromboembolism in adults admitted to hospital for the treatment of a recent medical illness.

**Reasons for negative opinion:** The EMA considered that the pivotal study was not reliable because some results of tests for blood clots were not available. In addition, patients treated with betrixaban had more episodes of bleeding than those treated with the comparator medicine. This was considered an important concern given that the medicine was expected to be used in patients with serious underlying conditions.

- ▶ [EMA. Refusal of the marketing authorisation for Dexxience \(betrixaban\). 23 March 2018.](#)  
[FDA approval of betrixaban \(BevyxXa®\): 23 June 2017.](#)

### Abaloparatide

**Product name:** Eladynos®

**Dosage form:** Injection for subcutaneous use

**Class:** Human parathyroid hormone-related peptide analog

**Regulatory authority:** EMA

**Use:** Treatment of postmenopausal women with osteoporosis at high risk for fracture.

**Reasons for negative opinion:** The EMA considered that the main study did not satisfactorily show the effectiveness of abaloparatide for the intended use. The data from two study sites had to be excluded as the study had not been conducted in compliance with good clinical practice at those sites. From

a safety point of view, the EMA was concerned about the medicine's effects on the heart, such as increases in heart rate and palpitations.

Because most post-menopausal women are at an increased risk of heart problems, the EMA could not identify a group of patients in whom the benefits would outweigh the risks.

- ▶ [EMA. Refusal of the marketing authorisation for Eladynos \(abaloparatide\). 23 March 2018.](#)  
[FDA approval of abaloparatide \(Tymlos®\). 28 April 2017.](#)

### Neratinib

**Product name:** Nerlynx®

**Dosage form:** Tablets

**Class:** Tyrosine kinase inhibitor;  
*ATC code:* L01XE45

**Regulatory authority:** EMA

**Intended use:** For the extended adjuvant treatment of early-stage, HER2-positive breast cancer in adult patients previously treated with trastuzumab.

**Reasons for negative opinion:** The EMA considered that, although more women on neratinib than on placebo lived for two years without disease progression than women (94% versus 92% respectively), it is uncertain that this difference would be seen in clinical practice. Furthermore, neratinib causes side effects in the digestive system, particularly diarrhoea, which affected most patients and might be difficult to manage.

- ▶ [EMA. Refusal of the marketing authorisation for Nerlynx \(neratinib\). 23 February 2018.](#)  
[FDA approval of neratinib maleate \(Nerlynx®\). 17 July 2017.](#)

## Publications and events

### Research and development

#### “Disease X” added to WHO research priority list

Geneva – In its annual review of its R&D Blueprint, WHO has added “Disease X” to the research priorities for pathogens that could cause serious epidemics and for which there are no or insufficient countermeasures. Disease X represents a known or unknown pathogen that is yet to be found to have potential to cause a serious international epidemic.

The list was first published in December 2015 and is reviewed annually. It now includes (in no particular order) Crimean-Congo haemorrhagic fever (CCHF), Ebola virus disease and Marburg virus disease, Lassa fever, Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS), Nipah and henipaviral diseases, Rift Valley fever (RVF), Zika, and Disease X. The R&D Blueprint explicitly seeks to enable cross-cutting preparedness that is also relevant for a future Disease X.

- ▶ WHO. List of Blueprint priority diseases [[webpage](#)].

#### Vaccines for emerging pathogens

In a recent article in JAMA, Dr Anthony Fauci and co-authors provide their views on the development of vaccines for emerging infectious diseases with pandemic potential. The authors conclude that the traditional approach of isolating and growing the pathogen does not support an effective response to these continually emerging

threats. They emphasize that it will be critical to exploit modern-day technological advances, pre-emptively establish detailed information on each family of viral pathogens, and invest in more infrastructure for surveillance in developing countries to expedite pathogen identification and jump-start the process of vaccine development.

- ▶ Graham BS, Mascola JR, Fauci AS. Novel Vaccine Technologies. Essential Components of an Adequate Response to Emerging Viral Diseases. JAMA. Published online March 22, 2018. doi:10.1001/jama.2018.0345.

### Access to medicines

#### European Parliament resolution

Brussels – The European Parliament has adopted a resolution calling for national and EU-wide measures to guarantee the right of patients to universal, affordable, effective, safe and timely access to essential and innovative therapies.<sup>(1)</sup> In its [Report on European Union \(EU\) Options for Improving Access to Medicines](#) the Committee on the Environment, Public Health and Food Safety points to the need for innovation with a clear clinical, social and economic added value, greater transparency of research data and costs; greater public investment in research; improved regulation and mechanisms to monitor conflicts of interest; and patient-oriented research priorities.

Health Action International (HAI) has commended the European Parliament for its report and has urged the European Commission and member states to follow

up on the recommendations in order to improve access to medicines in the EU.<sup>(2)</sup>

- ▶ <sup>(1)</sup> [European Parliament resolution of 2 March 2017 on EU options for improving access to medicines.](#)
- <sup>(2)</sup> [HAI Media statement, 3 March 2018.](#)

### The role of the pharmacist

The Hague – The International Pharmaceutical Federation (FIP) has published a report that highlights the important role of the pharmacist in ensuring access to safe and effective medicines in a variety of contexts.

Pharmacists are involved at all stages of the life cycle of medicines, from the production of raw materials through to their use by patients. In a landscape of challenges such as substandard and falsified medicines, globalization, and a shortage of human resources in health systems, the pharmacist's expertise is critical as part of a team approach to the management of medicines. Recognizing that regulation and supply systems have different levels of maturity in countries, the report emphasizes the importance of investments in further training and education to strengthen the competencies of health professionals in ensuring supply chain integrity and rational use of medicines.

- ▶ [FIP News, 8 May 2018.](#)  
FIP. [Pharmacists in the supply chain: The role of the medicines expert in ensuring quality and availability.](#) The Hague, the Netherlands: International Pharmaceutical Federation, 2018.

### Pharmaceutical waste management

#### Pharmaceutical pollution and AMR

Brussels – The European Public Health Alliance has published the report of a recent

event held to discuss the links between pharmaceutical pollution and antimicrobial resistance (AMR).<sup>(1)</sup> In Europe, pollution is mainly due to pharmaceutical consumption, while the contribution of manufacturing facilities is considered as negligible.<sup>(2)</sup> On the other hand, industrial pollution is a major problem in India, where pharmaceutical manufacturing is being stepped up to supply most of the world's generic medicines.<sup>(3)</sup> This has significant global impacts as the residues in the environment are becoming a reservoir for the development of resistant pathogens. A 2017 study of samples of effluent discharges in the Hyderabad area were found to have unexpectedly high levels of antibiotic residues and—correlated with this—high levels of resistant pathogens.<sup>(4)</sup>

The event participants recognized that manufacturing of pharmaceuticals in China and India is a problematic and growing issue that is fuelling AMR. It was proposed that this global issue should be addressed as part of the European strategy on Pharmaceuticals in the Environment (PiE), which is currently under public consultation <sup>(5)</sup> and is due to be released by May 2018. The participants concluded that, given the high costs of inaction on the closely connected challenges of PiE and AMR, a coherent policy with the right tools and instruments are urgently needed for action to be taken before the European Parliament elections in 2019.

- ▶ <sup>(1)</sup> [Joining the dots. Tackling Pharmaceuticals in the environment and AMR in Europe.](#) European Parliament, 30 January 2018. Event Report, March 2018.
- <sup>(2)</sup> [BIO Intelligence Service. Study on the environmental risks of medicinal products.](#) Final report. Prepared for the Executive Agency for Health and Consumers. 12 December 2013.
- <sup>(3)</sup> [Changing Markets Foundation. Hyderabad's pharmaceutical pollution crisis.](#) January 2018.

(4) Lübbert C, Baars C, Dayakar A *et al.* Environmental pollution with antimicrobial agents from bulk drug manufacturing industries in Hyderabad, South India, is associated with dissemination of extended-spectrum beta-lactamase and carbapenemase-producing pathogens. *Infection*. 2017 Aug;45(4):479-491.

(5) European Commission. Public consultation on pharmaceuticals in the environment.

### Medical waste in India increases

India – According to a recent study, India's medical waste is growing by 7% every year and will reach 775.5 tons by the year 2022. The study outlines the key challenges in biomedical waste management in India: slow data availability at state and central pollution control boards, underreporting of waste generated, limited handling capacity, unauthorized healthcare facility operations, and delays in developing biomedical waste treatment facilities in some states and territories.

The study report was released at a conference on biomedical waste management organized in New Delhi on 22 March 2018 by the Associated Chambers of Commerce & Industry of India (ASSOCHAM) in collaboration with the Directorate of Health Services within the Department of Health and Family Welfare of India. Releasing the report, Dr Kirti Bhushan, Director General of Health Services of the Delhi government stressed that safe and effective management of waste is not only a legal necessity but also a social responsibility.

- ▶ India's medical waste growing at 7% annually: ASSOCHAM. The Times of India. 22 March 2018.

## Diagnosics

### First WHO essential diagnostics list

Geneva – WHO has published its first Essential Diagnostics List (EDL). The list focuses on *in vitro* diagnostics (IVDs) and comprises 113 tests: 58 general IVDs for primary health care, and 55 tests for the detection, diagnosis and monitoring of global priority diseases including HIV, tuberculosis, malaria, hepatitis B and C, human papillomavirus and syphilis. The EDL describes IVDs according to their biological targets, indicating the test purpose, assay format, specimen type, and whether it is appropriate for primary health care or for health facilities with clinical laboratories. The list also provides links to WHO Guidelines or publications and, when available, to prequalified products.

The proposal for the first EDL was agreed by WHO's new Strategic Advisory Group of Experts on *In Vitro* Diagnostics (SAGE IVD) in response to a recommendation made by the WHO Expert Committee on the Selection of Essential Medicines at its 2017 meeting. It is intended as a reference for countries to update or develop their own list of essential diagnostics, alongside measures to ensure appropriate and quality-assured supplies, training of health care workers and safe use. WHO will expand the list over the next few years to include tests related to antimicrobial resistance, emerging pathogens, neglected tropical diseases and additional non-communicable diseases.

- ▶ WHO News release, 15 May 2018.

WHO. Executive summary. *World Health Organization Model List of Essential In Vitro Diagnostics*. First edition (2018). Report of the first Strategic Advisory Group on *In Vitro* Diagnostics (SAGE-IVD), WHO headquarters, Geneva, 16–20 April 2018.

## Disease updates

### **Ebola:** **Outbreak in DRC**

Geneva, Brazzaville, Kinshasa – A new Ebola outbreak has been reported from Bikoro in the Democratic Republic of the Congo (DRC). WHO is working with the Government of the DRC and a broad range of partners to rapidly scale up its operations and mobilize health partners, using the model of a successful response to a similar outbreak in 2017.<sup>(1)</sup>

As at 13 May there were 39 reported Ebola cases, including 2 confirmed, 20 probable (of which 18 were fatal), and 17 suspected cases. WHO has released US\$ 2.6 million from its Contingency Fund for Emergencies to support response activities. The estimated budget for an international response is US\$ 18 million for a three-month operation.<sup>(2)</sup>

► <sup>(1)</sup> WHO News release, 8 May 2018.

<sup>(2)</sup> WHO News release, 13 May 2018.

### **Dengue:** **Outbreak in La Réunion**

Geneva – WHO has been notified about a sharp increase of dengue fever in the French overseas territory of La Réunion in the Indian Ocean. As of 23 April, 1816 cases have been confirmed for the year 2018, including 428 probable and confirmed cases reported in the week of 16–23 April 2018 alone. In comparison, less than 100 cases were reported in all of 2017. The western and southern parts of the island are the most affected. The national authorities have stepped up their response and are implementing an emergency plan corresponding to a low level epidemic.

WHO has recommended a range of measures to reduce populations of mosquito

vectors and minimize individual exposure. The Organization advises against any travel or trade restrictions at this stage.

► WHO Disease outbreak news, 1 May 2018.

### **Yellow fever:** **Strategy to end epidemics**

Abuja – WHO and the Ministry of Health of Nigeria have launched the “Eliminate Yellow fever Epidemics (EYE) in Africa” strategy, which aims to end yellow fever epidemics in Africa through vaccination campaigns and routine immunization, prevention of international spread, and rapid containment of outbreaks. By 2026, nearly one billion people are to be vaccinated against yellow fever in 27 high-risk African countries. The campaign will be supported by WHO, Gavi – the Vaccine Alliance, UNICEF and more than 50 health partners.

In recent years yellow fever has re-emerged as a serious global public health threat. The ease and speed of population movements, rapid urbanization and a resurgence of mosquitoes due to global warming have significantly increased the risk of urban outbreaks with international spread.

► WHO News release, 10 April 2018.

### **Cholera:** **Largest-ever vaccine drive**

Geneva, Brazzaville – A spate of cholera outbreaks across Africa has prompted the largest cholera vaccination drive in history, with more than two million people to receive oral cholera vaccine. Major campaigns are under way in Zambia, Uganda, Malawi, South Sudan and Nigeria. The vaccines are sourced from the global stockpile, which is managed by the Global Task Force on Cholera Control (GTFCC) and funded by Gavi, the Vaccine Alliance.<sup>(1)</sup>



A resolution on cholera was endorsed at the 71st World Health Assembly, urging cholera-affected countries to implement a roadmap that aims to reduce deaths from the disease by 90% by 2030.(2)

► (1) [WHO News release, 7 May 2018.](#)

(2) [WHO News release, 24 May 2018.](#)

### **Hepatitis C:** **Treatment access increasing**

Geneva – WHO has published an update to its 2016 report on access to treatment of hepatitis C virus (HCV) infection. Access to life-saving direct-acting antivirals (DAA) is still low, but is increasing in champion countries such as Egypt, Pakistan, Brazil, China and Georgia. Drawing on surveys in 23 low- and middle-income countries and among innovator and generic companies, as well as interviews and other new data, the report looks at the key factors that determine access to DAA medicines and highlights areas for action by ministries of health and other government decision-makers, pharmaceutical manufacturers and technical partners.(1)

With the advent of DAAs, HCV infection has become curable. As the cost of the medicines is coming down, treatment becomes cost-saving because it substantially reduces the burden of liver cirrhosis and cancer as well as diseases such as depression and diabetes. New evidence suggests that all people aged 12 or above diagnosed with chronic HCV (with the exception of pregnant women) should be offered treatment. WHO expects to release new HCV treatment guidelines soon.(2)

► (1) [WHO. Progress report on access to hepatitis C treatment. Focus on overcoming barriers in low- and middle-income countries. March 2018.](#)

(2) [WHO. Hepatitis C: simplified curative treatments can drive global scale-up. 13 April 2018.](#)

### **Tuberculosis:** **World's biggest infectious killer**

Brussels – On the eve of World Tuberculosis Day, four European Commissioners have underlined the EU's commitment to ending the tuberculosis epidemic by 2030 and have called on governments all over the world to redouble their efforts and make this happen. The EU is also working to address antimicrobial resistance, which is inextricably linked to tuberculosis, as well as the social conditions that encourage the disease to spread.(1)

Geneva – WHO and the Stop TB Partnership have launched the first-ever joint advocacy and communications campaign to support thousands of partners, activists and persons affected by tuberculosis. The disease remains among the top 10 causes of death worldwide, and is the major cause of deaths related to antimicrobial resistance and the leading killer of people with HIV. To commemorate World Tuberculosis Day, the partners have provided a joint advocacy and communications toolkit containing practical guidance and information.(2)

Geneva – Based on an expedited review of preliminary results from the STREAM Stage 1 randomized controlled trial, WHO has advised national tuberculosis programmes and other stakeholders to continue using the shorter regimens lasting 9–12 months to treat multi-drug-resistant tuberculosis.(3)

WHO has also provided recommendations for the management of isoniazid-resistant tuberculosis.(4) Consolidated guidelines and an update of the *Companion Handbook to the WHO guidelines for the management of drug-resistant tuberculosis* are planned to be released later in 2018.

At the 71<sup>st</sup> World Health Assembly, held in May 2018 in Geneva, delegates agreed on a resolution committing Member States to accelerate their actions to end tuberculosis. The resolution also requests the Secretariat to develop a new global strategy for tuberculosis research and innovation.<sup>(5)</sup>

- ▶ (1) [European Commission Statement](#), 23 March 2018.
- (2) [WHO TB News](#), 2 March 2018.
- (3) [WHO. Position statement on the continued use of the shorter MDR-TB regimen following an expedited review of the STREAM Stage 1 preliminary results](#). April 2018.
- (4) [WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis](#). 2018.
- (5) [WHO News release](#), 24 May 2018.

### **Non-communicable diseases: Major health gains from investments**

Geneva – A new WHO report shows that even modest investments into actions to address non-communicable diseases (NCDs) generate significant benefits. In low- and lower middle-income countries (LLMICs), where almost half of all premature deaths from NCDs occur, every dollar invested will yield a return to society of at least US\$ 7 in increased employment, productivity and longer life. Among the most cost-effective interventions are increasing taxes on tobacco and alcohol, reducing salt content in food products, providing medicinal therapy and counselling to people who have had a heart attack or stroke, vaccinating girls aged 9–13 years against human papillomavirus, and screening women aged 30–49 years for cervical cancer. However, global financing to combat NCDs is severely limited. The report calls on donors to provide kick-start funding

to governments of LLMICs for ambitious scaling-up of “best buy” policies.

- ▶ [WHO News release](#), 16 May 2018.
- [WHO. Saving lives, spending less: a strategic response to NCDs](#). 2018.

### **HTLV-1: A scourge yet to be addressed**

Sixty representatives from 26 countries have signed an open letter calling for WHO’s support to help prevent the transmission of human T-cell lymphotropic virus type 1 (HTLV-1), a virus similar to HIV and transmitted by the same routes. HTLV-1 is the most potent carcinogenic oncovirus, and potentially the most oncogenic risk factor including chemical carcinogens. Although it was discovered almost 40 years ago, effective intervention strategies have not been actively publicized. The authors warn that HTLV-1 remains a strong threat to individual and community health, and even more so to global health because of the accelerated rate of human migration in recent times.

The letter proposes a WHO vision for the prevention of HTLV-1 transmission, with five intervention strategies to reduce the incidence of HTLV-1 infection. These are based on evidence that transmission can be averted by condom use, by avoiding the transfusion and transplantation of infected blood and organs, by avoiding breastfeeding (if deemed safe) or reducing its duration to 3–6 months, by using sterile needles, and by educating healthcare professionals and the population about prevention strategies.

- ▶ Martin F, Tagaya Y, Gallo R. Time to eradicate HTLV-1: an open letter to WHO. *The Lancet*. 2018; 391 (10133): 1893–4. DOI: [https://doi.org/10.1016/S0140-6736\(18\)30974-7](https://doi.org/10.1016/S0140-6736(18)30974-7)

## WHO updates

### 71<sup>st</sup> World Health Assembly

Geneva – The 71<sup>st</sup> World Health Assembly was held on 21–26 May 2018 in Geneva, Switzerland. Delegates adopted an ambitious strategic “triple billion” five-year plan which aims to ensure that by 2023 one billion more people benefit from universal health coverage; one billion more people are better protected from health emergencies; and one billion more people enjoy better health and wellbeing.<sup>(1)</sup> Several of the decisions and resolutions agreed upon at the Assembly were related to improving access to quality-assured medical products.

#### Access to medicines

The delegates asked WHO to elaborate a five-year roadmap to increase access to safe and effective essential medicines, vaccines and other health products – something that is becoming increasingly challenging across economic settings as medicines prices are rising. Member States also urged stakeholders to implement the recommendations for priority actions under WHO’s Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property, as identified in the review panel’s report.<sup>(2)</sup>

#### Specific medical products

The Member States adopted a landmark resolution on **containment of poliovirus materials** under strict biosafety and biosecurity handling and storage conditions in a limited number of facilities that serve critical functions in vaccine production or research.<sup>(3)</sup> They further agreed on a resolution for a coordinated global response to **rheumatic heart disease**, including by ensuring a consistent supply of quality-assured antibiotics.<sup>(4)</sup> Resolutions were also adopted regarding **tuberculosis** (see page

223–224) and **cholera** (see page 223), and regarding **snakebite**, underlining the urgent need to improve access to safe, effective and affordable antivenoms.<sup>(4)</sup> Resolutions were furthermore adopted to improve access to **assistive technology** such as wheelchairs or hearing aids, and **digital technologies** for example to track disease outbreaks or send mobile phone text messages for positive behaviour change.<sup>(4)</sup>

#### Public health preparedness

Delegates welcomed a proposed five-year global strategic plan to improve public health preparedness and response through the implementation of the **International Health Regulations (IHR)**, a legal instrument introduced in 2007 that is binding on 196 countries and WHO in their work to uphold global public health security.<sup>(4)</sup> An update was provided on the new **Ebola** outbreak (see page 222) and on the systems put in place for a faster and more predictable response than during the previous outbreak.<sup>(2)</sup> Delegates also approved the recommendations of the Review of the **Pandemic Influenza Preparedness Framework**.<sup>(4)</sup> On the margins of the Assembly, WHO and the World Bank Group launched the Global Preparedness Monitoring Board as a new mechanism to ensure stringent independent monitoring and regular reporting to tackle outbreaks, pandemics, and other emergencies with health consequences.<sup>(5)</sup>

- ▶ <sup>(1)</sup> WHO News release, 23 May 2018.
- <sup>(2)</sup> WHO News release, 23 May 2018 (2).
- <sup>(3)</sup> WHO News release, 26 May 2018.
- <sup>(4)</sup> WHO News release, 25 May 2018.
- <sup>(5)</sup> WHO News release, 24 May 2018.

The meeting documents are available at:  
[http://apps.who.int/gb/e/e\\_wha71.html](http://apps.who.int/gb/e/e_wha71.html)

## WHO prequalification updates

### ICH Q3D introduced for APIs

#### What is ICH Q3D?

The [ICH Q3D guideline](#) presents a process to assess and control elemental impurities in drug products using the principles of risk assessment.

#### How will it be used in prequalification?

The ICH Q3D risk assessment includes consideration of the impurity profile of the active pharmaceutical ingredient (API). Therefore, the WHO Prequalification Team (PQT) has decided to adopt the ICH Q3D guideline for the assessment of the elemental impurities information in new applications for both procedures: the API master file (APIMF) procedure and the procedure for prequalification of APIs. The implementation of ICH Q3D for finished pharmaceutical products (FPPs) is still under consideration within PQT.

#### Must a risk assessment be provided?

Since the ICH Q3D guideline applies to the finished product, providing a risk assessment as part of the APIMF procedure is not a mandatory requirement. However, many API manufacturers may wish to undertake a risk assessment in order that this may then be used in an assessment of the finished pharmaceutical product with respect to ICH Q3D.

Therefore when submitting an APIMF, either through the APIMF procedure or as part of the API Prequalification procedure, the applicant has two possibilities:

- **Option 1:** Do not provide a risk management summary (RMS); or
- **Option 2:** Provide a risk management summary (RMS) for elemental impurities that may be present in the final API.

Applicants should indicate the selected option on the application form.

#### What will happen during assessment?

→ If no RMS is provided, only the elemental impurities that have been intentionally added will be investigated as part of the assessment, and the need for inclusion of controls for elemental impurities in the API specifications will be determined on this basis.

→ If an RMS is provided then this will be considered as part of an assessment in line with ICH Q3D:

**For an APIMF participating only in the APIMF procedure,** the outcome of the RMS assessment will be recorded in the internal assessment report and remain available if needed for reference as part of an FPP assessment.

**For APIs seeking prequalification,** a statement indicating whether a risk assessment for elemental impurities has been provided will be mentioned on the Confirmation of API Prequalification document (CPQ). In case an RMS is submitted it will be annexed to the CPQ.

#### What about APIMFs that are already under assessment?

For those APIMFs that have already been accepted for assessment, the applicant can submit an RMS for elemental impurities at any time through the amendment procedure. There is no specific change category in the APIMF amendments guideline for such a revision, but applicants should submit such a change as 11 (AIN). However for ongoing applications it should not be provided as part of responses, since these invariably delay the completion of the application.

- ▶ [WHO/PQT–medicines. Guidance document, 23 May 2018.](#)

**New WHO stability guideline published**

The updated WHO stability guideline has now been published in the [WHO Technical Report Series \(TRS\) No. 1010, Annex 10](#). This guideline replaces the previous stability guideline in TRS 953 Annex 2 (2009) and should be taken into account in preparing the quality part of product dossiers for prequalification.

► [WHO Prequalification News, 7 June 2018](#).

**“Firsts”**

- **First flucytosine product** prequalified (HA693). Flucytosine is used to treat cryptococcal disease and other HIV/AIDS-related fungal infections.
- **First dispersible ethambutol tablets** for children prequalified (TB334). Ethambutol is used in the treatment of tuberculosis.
- **First amikacin injection** prequalified (TB319). Amikacin is used for second-line treatment of tuberculosis.

► [WHO. List of prequalified Medicines/Finished Pharmaceutical Products](#)

- **First Quality Control Laboratory (QCL) in sub-Saharan West Africa** prequalified: United States Pharmacopoeia (USP) Ghana. This is also a first under the USP banner.

► [WHO. List of prequalified Quality Control Laboratories](#).

- **First Medicines Quality Workshop for Manufacturers**, held on 4–6 July 2018 in Copenhagen, Denmark. This new type of workshop is aimed at manufacturers that are participating, or intend to participate, in medicines prequalification. The speakers are senior WHO prequalification assessors.

► [WHO Prequalification of medicines website. Events. First PQT Medicines Quality Workshop for Manufacturers](#).

**Additional medicines invited****Anti-tuberculosis medicines**

- Bedaquiline (fumarate), tablet 100mg\*
- Delamanid, tablet 50mg\*
- Delamanid, tablet 50mg (dispersible)\*
- Rifapentine, tablet 300 mg\*\*
- Isoniazid 150 mg/rifapentine 150 mg and Isoniazid 300 mg/rifapentine 300 mg (preferably dispersible or crushable tablets in fixed-dose combination format)\*\*
- Rifapentine, tablet 150 mg (dispersible)\*\*
- Rifapentine, tablet 300 mg (scored and dispersible)\*\*

► \* [16<sup>th</sup> Invitation to Manufacturers of Antituberculosis Medicines](#), 6 March 2018.

\*\* [17<sup>th</sup> Invitation to Manufacturers of Antituberculosis Medicines](#), 26 March 2018.

**Anti-malarial medicines**

Additional product:

- Artesunate/pyronaridine tablet 20mg/60mg (preferably dispersible)

Additional product strengths:

- Dihydroartemisinin/piperaquine phosphate tablet 60mg/480mg
- Dihydroartemisinin/piperaquine phosphate tablet 30mg/240mg (preferably dispersible)

► [16<sup>th</sup> Invitation to Manufacturers of Antimalarial Medicines](#), 16 March 2018.

Coming soon: [Biosimilars](#)

**Pakistan joins collaborative registration**

The regulatory authority of Pakistan is the 34<sup>th</sup> authority to join the WHO's collaborative registration procedure. The purpose of this procedure is to shorten the time to registration of WHO-prequalified medicines to a target period of 90 days, based on confidential sharing of WHO assessment and inspection reports with permission of the manufacturer.

► [WHO Prequalification News, 18 April 2018](#).  
[WHO Prequalification website. Accelerated Registration of Prequalified FPPs](#).

## Upcoming events

### August

#### WHO-UMC-HSA Inter-Regional Pharmacovigilance Training workshop

Singapore, 15–17 August 2018

Expert pharmacovigilance trainers from WHO, the Uppsala Monitoring Centre (UMC), and the Health Sciences Authority (HSA) of Singapore will share with participants their expertise and experience over a three-day workshop, jointly organized with the WHO, UMC, HSA, and the Duke-NUS Medical School's Centre of Regulatory Excellence (CoRE) in Singapore. The workshop is part of a continuation of efforts to enhance pharmacovigilance capabilities in the ASEAN region.

Given this year's underlying theme of *Partnerships to Protect Public Health*, the organizers welcome participation from non-regulators, such as people from the industry and non-government organizations (NGOs).

► [www.duke-nus.edu.sg/core/event/who-umc-hsa-inter-regional-pharmacovigilance-training-workshop](http://www.duke-nus.edu.sg/core/event/who-umc-hsa-inter-regional-pharmacovigilance-training-workshop)

### September

#### 78<sup>th</sup> FIP World Congress of Pharmacy and Pharmaceutical Sciences

Glasgow, United Kingdom, 2–6 September 2018

The 2018 FIP congress in Glasgow, Scotland, invites pharmacy practitioners and pharmaceutical scientists from around the world to come together to consider ways of extending the role of pharmacists so that they play a full part in ensuring that patients and health systems achieve full benefit from the medicines people take. The one-size-fits-all approach is clearly

failing many patients around the globe for the pharmacological treatment of disease. Pharmacists and pharmaceutical scientists are uniquely trained and qualified health care professionals capable of personalising therapy for improving patient outcomes.

► [www.fip.org/glasgow2018/](http://www.fip.org/glasgow2018/)

#### 18<sup>th</sup> International Conference of Drug Regulatory Authorities (ICDRA)

Dublin, Ireland, 3–7 September 2018

The 18<sup>th</sup> ICDRA will be organized around the theme *Smart Safety surveillance: A life-cycle approach to promoting safety of medical products*. The pre-ICDRA event on 3–4 September is open to all interested stakeholders. The ICDRA conference will be held on 5–7 September and is open to representatives of governments and national regulatory authorities.

► [www.icdra2018.ie/](http://www.icdra2018.ie/)

HPRA. *Invitation to Exhibit at the HPRA PRE-ICDRA conference 3-4 September 2018.*

#### Joint UNFPA-UNICEF-WHO meeting

Copenhagen, Denmark, week of 24 September 2018

The Joint UNICEF-UNFPA-WHO Meeting with manufacturers and suppliers of *in vitro* diagnostic, vaccines, finished pharmaceutical products, active pharmaceutical ingredients, contraceptive devices and vector control products will provide updates on UN-funded procurement, prequalification and cross-cutting issues. There will be opportunities for one-to-one discussions.

► [extranet.who.int/prequal/events/2018-unicef%E2%80%93unfpa%E2%80%93who-meeting-pre-announcement](http://extranet.who.int/prequal/events/2018-unicef%E2%80%93unfpa%E2%80%93who-meeting-pre-announcement)

# Consultation documents

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

## The International Pharmacopoeia

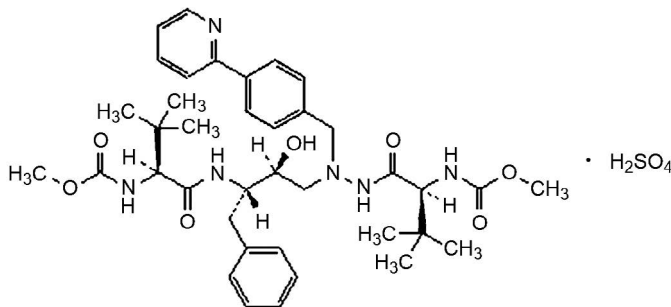
### Atazanavir sulfate (Atazanaviri sulfas)

This is a draft proposal of a revised monograph for *The International Pharmacopoeia* (Working document QAS/17.738, March 2018). The working document with line numbers and tracked changes is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).

**[Note from the Secretariat:** Following laboratory investigations performed to establish Atazanavir sulfate ICRS it is proposed to revise the monograph on Atazanavir sulfate with a view to:

- change the recrystallization solvent used in identity test A by IR (from methanol to acetone); and
- update the style of the monograph.

In the text available at the above-mentioned website, changes from the current monograph are indicated in the text by insert or ~~delete~~.]



**Molecular formula.** C<sub>38</sub>H<sub>52</sub>N<sub>6</sub>O<sub>7</sub> · H<sub>2</sub>O<sub>4</sub>S

**Relative molecular mass.** 802.9

**Chemical names.** Dimethyl (3S,8S,9S,12S)-9-benzyl-3,12-di-*tert*-butyl-8-hydroxy-4,11-dioxo-6-[[4-(pyridin-2-yl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioate monosulfate; 2,5,6,10,13-Pentaazatetradecanedioic acid,



**Atazanavir sulfate (Ph. Int.)**

3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-, 1,14-dimethyl ester, (3S,8S,9 S,12S)-, sulfate (1:1); CAS Reg. No. 229975-97-7.

**Description.** A white to a pale yellow powder.

**Solubility.** Freely soluble in methanol, practically insoluble in water.

**Category.** Antiretroviral (protease inhibitor).

**Storage.** Atazanavir sulfate should be kept in a tightly closed container.

**Additional information.** Atazanavir sulfate is slightly hygroscopic and may exhibit polymorphism.

**Requirements**

Atazanavir sulfate contains not less than 98.0% and not more than 102.0% of  $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$ , calculated with reference to the dried substance.

**Identity tests**

- Either test A and D or test B, C and D should be applied.
- A. Carry out the examination as described under [1.7 Spectrophotometry in the infrared region](#). The infrared absorption spectrum is concordant with the spectrum obtained from atazanavir sulfate RS or with the *reference spectrum* of atazanavir sulfate.

If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the test substance and atazanavir sulfate RS in a small amount of acetone R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from atazanavir sulfate RS.
- B. Carry out test B.1, or where ultraviolet (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 9.5 volumes of dichloromethane R and 0.5 volume of 2-propanol R as the mobile phase. Apply separately to the plate 10  $\mu$ L of each of the following 2 solutions in methanol R. For solution (A) use 1 mg of the test substance per mL. For solution (B) use 1 mg of atazanavir sulfate RS per mL. After removing the plate from the chromatographic chamber allow it to dry exhaustively in air or in a current of air.

Examine the chromatogram in UV light (254 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).
  - B.2 Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using the conditions described under test B.1, but using a plate containing silica gel R5 as the coating substance.

Spray the plate with basic potassium permanganate (~5 g/L) TS. Examine the chromatogram in daylight. The principal spot obtained with solution (A) corresponds in position, appearance and intensity to that obtained with solution (B).

## Atazanavir sulfate (Ph. Int.)

- C. The absorption spectrum of a 10 µg/mL solution of the test substance in methanol R, when observed between 230 nm and 340 nm, exhibits two maxima at about 250 nm and 280 nm.
- D. A 20 mg/mL solution of the test substance yields reaction A described under [2.1 General identification tests](#) as characteristic of sulfates.

**Heavy metals.** [2.2.3 Limit test for heavy metals](#)

**Sulfated ash** ([2.3](#)). Not more than 2.0 mg/g.

**Loss on drying.** Dry for 3 hours at 105°C; it loses not more than 10.0 mg/g.

**Specific optical rotation.** Use a 10 mg/mL solution in equal volumes of methanol R and water R at 22°C and calculate with reference to the dried substance; the specific optical rotation is between -44° and -48°.

**Related substances**

Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (150 mm × 4.6 mm) packed with end-capped, base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 µm). Use the following conditions for gradient elution:

mobile phase A: 0.02 M phosphate buffer pH 3.5, acetonitrile R (70:30 v/v);

mobile phase B: 0.02 M phosphate buffer pH 3.5, acetonitrile R (30:70 v/v).

Prepare the 0.02 M phosphate buffer pH 3.5 by dissolving 2.72 g of anhydrous potassium dihydrogen phosphate R in 800 mL of water R, adjust the pH to 3.5 by adding phosphoric acid (~105 g/L) TS and dilute to 1000 mL with water R.

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–2	100	0	Isocratic
2–10	100 to 75	0 to 25	Linear gradient
10–30	75 to 50	25 to 50	Linear gradient
30–45	50 to 0	50 to 100	Linear gradient
45–50	0	100	Isocratic
50–52	0 to 100	100 to 0	Linear gradient
52–60	100	0	Isocratic

Prepare the following solutions using as diluent a mixture of equal volumes of water R and acetonitrile R. For solution (1) dissolve about 50 mg of the test substance and dilute to 50.0 mL. For solution (2) dilute 10.0 mL of solution (1) to 200.0 mL. Dilute 10.0 mL of this solution to 100.0 mL. For solution (3) mix 1 mL of solution (1) with 4.5 mL of water R and 0.5 mL of sodium hydroxide (10 g/L) TS and heat the mixture in a water-bath at 85°C for 15 minutes.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 250 nm. Maintain the column at a temperature of 30°C.

**Atazanavir sulfate (Ph. Int.)**

Inject 20 µL of solution (3). The test is not valid unless the resolution between the peak due to atazanavir (retention time about 22 minutes) and the peak with a relative retention of about 1.2 is at least 4.

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

In the chromatograms obtained with test solution (1):

- the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);
- the sum of the areas of all peaks, other than the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).  
Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

**Assay**

Dissolve 0.300 g, accurately weighed, in 30 mL of methanol R by sonication for 10 minutes. Then add 30 mL of water and titrate with sodium hydroxide (0.1 mol/L) VS, determining the end-point potentiometrically. Each mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 40.145 mg of  $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$ .

\*\*\*

## Atazanavir capsules (*Atazanaviri capsulae*)

**This is a draft proposal of a revised monograph for *The International Pharmacopoeia* (Working document QAS/17.739, March 2018). The working document with line numbers and tracked changes is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).**

**[Note from the Secretariat:** Following laboratory investigations performed to establish Atazanavir sulfate ICRS it is proposed to revise the monograph on Atazanavir capsules with a view to:

- update the information given under Additional information to reflect the information given in the 20th WHO Model List of Essential Medicines; and
- use the absorptivity value of atazanavir sulfate to calculate the result of the dissolution test and assay method B.

In the text available at the above-mentioned website, changes from the current monograph are indicated in the text by insert or delete.]

**Category.** Antiretroviral (protease inhibitor).

**Storage.** Atazanavir capsules should be kept in a tightly closed container.

**Additional information.** Strength in the current WHO Model List of Essential Medicines (EML): 100 mg, 300 mg of atazanavir (as sulfate). Strength in the current WHO EML for Children: 100 mg of atazanavir (as sulfate).

### Requirements

Comply with the monograph for Capsules.

### Definition

Atazanavir capsules contain atazanavir sulfate. They contain not less than 90.0% and not more than 110.0% of the amount of atazanavir,  $C_{38}H_{52}N_6O_7$ , stated on the label. Each mg of atazanavir ( $C_{38}H_{52}N_6O_7$ ) is equivalent to 1.139 mg of atazanavir sulfate ( $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$ ).

### Identity tests

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

- A.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 9.5 volumes of dichloromethane R and 0.5 volume of 2-propanol R as the mobile phase. Apply separately to the plate 10  $\mu$ L of each of the following 2 solutions in methanol R. For solution (A) disperse a quantity of the content of the capsules containing about 20 mg of atazanavir in 10 mL of methanol R, sonicate for 10 minutes, allow to cool to room temperature, dilute to 20 mL, filter and use the filtrate. For solution (B) use 1.1 mg of atazanavir sulfate RS per mL.

**Atazanavir capsules (Ph. Int.)**

After removing the plate from the chromatographic chamber allow it to dry exhaustively in air or a current of air. Examine the chromatogram in ultraviolet light (254 nm).

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

A.2 Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using the conditions described above under test A.1 but using a plate containing silica gel R5 as the coating substance. Spray with basic potassium permanganate (~5 g/L) TS. Examine the chromatogram in daylight.

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

- B. Disperse a quantity of the content of the capsules containing about 20 mg of atazanavir in 10 mL of methanol R, sonicate for 10 minutes, allow to cool to room temperature, dilute to 20 mL and filter. Dilute 1.0 mL of the filtrate to 100.0 mL with methanol R. The absorption spectrum ([1.6](#)) of the resulting solution, when observed between 230 and 340 nm, exhibits two maxima at about 250 nm and 280 nm.
- C. To a quantity of the content of the capsules equivalent to 0.2 g of atazanavir add 10 mL of a mixture of 1 volume of water R and 1 volume of acetonitrile R, shake and filter. The filtrate yields Reaction A described under [2.1 General identification tests](#) as characteristic of sulfates.

**Dissolution**

Carry out the test as described under [5.5 Dissolution test for solid oral dosage forms](#) using as the dissolution medium 900 mL of dissolution buffer pH 2.5 TS and rotating the paddle at 50 revolutions per minute. At 45 minutes withdraw a sample of 10.0 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature. Dilute a suitable volume of the filtrate with dissolution medium to obtain a solution containing 0.10 mg of atazanavir per mL. Measure the absorbance ([1.6](#)) of a 1 cm layer of the resulting solution at the maximum at about 250 nm, using the dissolution medium as the blank. For each of the capsules tested, calculate the total amount of atazanavir ( $C_{38}H_{52}N_6O_7$ ) in the medium, using an absorptivity value of 11.4 for atazanavir sulfate ( $A_{1cm}^{1\%} = 114$ ). Each mg of atazanavir sulfate ( $C_{38}H_{52}N_6O_7 \cdot H_2SO_4$ ) is equivalent to 1.139 mg of atazanavir ( $C_{38}H_{52}N_6O_7$ ).

Evaluate the results as described under [5.5 Dissolution test for solid dosage forms, Acceptance criteria](#). The amount in solution for each capsule is not less than 75% (Q) of the amount stated on the label.

**Related substances**

Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (150 mm × 4.6 mm) packed with end-capped base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 μm). Use the following conditions for gradient elution:

## Atazanavir capsules (Ph. Int.)

mobile phase A: 0.02 M phosphate buffer pH 3.5, acetonitrile R (70:30 v/v);

mobile phase B: 0.02 M phosphate buffer pH 3.5, acetonitrile R (30:70 v/v).

Prepare the 0.02 M phosphate buffer pH 3.5 by dissolving 2.72 g of anhydrous potassium dihydrogen phosphate R in 800 mL of water R, adjust the pH to 3.5 by adding phosphoric acid (~105 g/L) and dilute to 1000 mL with water R.

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–2	100	0	Isocratic
2–10	100 to 75	0 to 25	Linear gradient
10–30	75 to 50	25 to 50	Linear gradient
30–45	50 to 0	50 to 100	Linear gradient
45–50	0	100	Isocratic
50–52	0 to 100	100 to 0	Linear gradient
52–60	100	0	Isocratic

Prepare the following solutions using as diluent a mixture of equal volumes of acetonitrile R and water R. For solution (1) weigh and mix the contents of 20 capsules. Transfer a quantity of the mixed contents equivalent to 20 mg of atazanavir into a 20 mL volumetric flask. Add about 10 mL of the diluent, sonicate for 10 minutes, allow to cool to room temperature, make up to volume and filter. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3) mix 1 mL of solution (1) with 4.5 mL of water R and 0.5 mL of sodium hydroxide (10 g/L) TS and heat the mixture in a water bath at 85°C for 15 minutes.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 250 nm. Maintain the column at a temperature of 30°C.

Inject 20 µL of solution (3). The test is not valid unless the resolution between the peak due to atazanavir (retention time about 22 minutes) and the peak with a relative retention of about 1.2 is at least 4.

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

In the chromatograms obtained with test solution (1):

- the area of any peak, other than the principal peak, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);
- the sum of the areas of all peaks, other than the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

## Atazanavir capsules (Ph. Int.)

**Assay**

- Either test A or test B may be applied.
- A. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (150 mm × 4.6 mm) packed with end-capped base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (5 μm).

As the mobile phase use a solution prepared as follows: 60 volumes of acetonitrile R and 40 volumes of 0.02 M phosphate buffer pH 3.5. Prepare the 0.02 M phosphate buffer pH 3.5 according to the procedure described in the related substances test.

Prepare the following solutions using as diluent a mixture of equal volumes of acetonitrile R and water R. For solution (1) weigh and mix the contents of 20 capsules. Transfer a quantity equivalent to 20.0 mg of atazanavir, accurately weighed, into a 20 mL volumetric flask. Add about 10 mL of the diluent, sonicate for about 10 minutes, allow to cool to room temperature and make up to volume. Filter a portion of this solution, discarding the first few mL. Dilute 5.0 mL of the filtrate to 50.0 mL with the diluent. For solution (2) use 0.11 mg of atazanavir sulfate RS per mL.

Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 250 nm. Maintain the column at a temperature of 30°C.

Inject alternately 20 μL each of solutions (1) and (2) and record the chromatograms for 1.5 times the retention time of atazanavir (about 4 minutes).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of atazanavir, (C<sub>38</sub>H<sub>52</sub>N<sub>6</sub>O<sub>7</sub>) in the capsules, using the declared content of C<sub>38</sub>H<sub>52</sub>N<sub>6</sub>O<sub>7</sub> in atazanavir sulfate RS.

- B. Weigh and mix the contents of 20 capsules. Transfer a quantity equivalent to 20 mg of atazanavir, accurately weighed, to a 20 mL volumetric flask. Add about 10 mL of methanol R, sonicate for about 10 minutes, allow to cool to room temperature and make up to volume with methanol R. Filter a portion of this solution, discarding the first few mL of the filtrate. Dilute 1.0 mL of the filtrate to 10.0 mL with methanol R. Measure the absorbance ([1.6](#)) of a 1 cm layer of this solution in at the maximum at about 250 nm, using methanol R as a blank. Calculate the percentage content of C<sub>38</sub>H<sub>52</sub>N<sub>6</sub>O<sub>7</sub> in the capsules using an absorptivity value of 14.5 for atazanavir sulfate ( $A_{1\text{cm}}^{1\%} = 145$ ). Each mg of atazanavir sulfate (C<sub>38</sub>H<sub>52</sub>N<sub>6</sub>O<sub>7</sub> • H<sub>2</sub>SO<sub>4</sub>) is equivalent to 1.139 mg of atazanavir (C<sub>38</sub>H<sub>52</sub>N<sub>6</sub>O<sub>7</sub>).

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## Daclatasvir dihydrochloride (*Daclatasviri dihydrochloridum*)

This is a draft proposal of a monograph for *The International Pharmacopoeia* (Working document QAS/18.762, May 2018). The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).

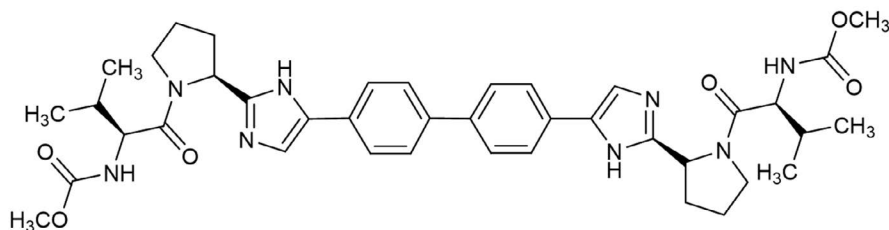
**[Note from the Secretariat.** The monograph on Daclatasvir dihydrochloride is proposed for inclusion in *The International Pharmacopoeia*.

The methods and specifications were drafted based on information provided by manufacturers and found in the scientific literature and on laboratory investigations.]

**Molecular formula.** C<sub>40</sub>H<sub>50</sub>N<sub>8</sub>O<sub>6</sub>·2HCl

**Relative molecular mass.** 811.81

**Graphic formula**



**Chemical name.** Methyl *N*-[(2*S*)-1-[(2*S*)-2-[5-[4-[4'-[2-[(2*S*)-1-[(2*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1*H*-imidazol-5-yl]phenyl]phenyl]-1*H*-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate dihydrochloride; CAS Reg. No. 1009119-65-6

**Description.** A white to a pale yellow powder.

**Solubility.** Freely soluble in water, soluble in methanol and very slightly soluble in dimethylformamide.

**Category.** Antiviral (nonstructural protein 5A inhibitor).

**Storage.** Daclatasvir dihydrochloride should be kept in a tightly closed container.

**Additional information.** Daclatasvir dihydrochloride may exhibit polymorphism.

### Requirements

**Manufacture.** The production method is validated to demonstrate that genotoxic halogenated biphenyl derivatives are adequately controlled in the final product.

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**Daclatasvir dihydrochloride (Ph. Int.)**

**Definition.** Daclatasvir dihydrochloride contains not less than 97.0% and not more than 102.0% (“Assay”, method A) or not less than 98.0% and not more than 102.0% (“Assay”, method B) of  $C_{40}H_{50}N_8O_6 \cdot 2HCl$ , calculated with reference to the anhydrous substance.

**Identity tests**

- Either tests A, E and F or tests D, E and F together with any one of tests B or C may be applied.

A. Carry out the examination as described under [1.7 Spectrophotometry in the infrared region](#). The infrared absorption spectrum is concordant with the spectrum obtained from daclatasvir dihydrochloride RS or with the *reference spectrum* of daclatasvir dihydrochloride.

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

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

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

C.1 Carry out test as described under [1.14.1 Thin-layer chromatography](#) using silica gel R4 or similar as the coating substance and a mixture of 77 volumes of ethyl acetate R, 15 volumes of methanol R and 8 volumes of water R as the mobile phase. Apply separately to the plate 2  $\mu$ L of each of the following 2 solutions in methanol R containing (A) 10 mg of the test substance per mL and (B) 10 mg of daclatasvir dihydrochloride RS per mL. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of cool air. Examine the chromatogram in ultraviolet light (365 nm).

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

C.2 Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using the conditions described above under C.1. After drying the plate spray with basic potassium permanganate (5 g/L) TS. Examine the chromatogram in daylight.

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

D. The absorption spectrum ([1.6](#)) of a 10  $\mu$ g per mL solution of the test substance in methanol R, when observed between 230 nm and 400 nm, exhibits one maximum at 314 nm.

E. Determine the specific optical rotation ([1.4](#)) using a 10 mg per mL solution of the test substance in methanol R. Calculate with reference to the anhydrous substance:  $[\alpha]_D^{25} = -92.0$  to  $-102.0$ .

## Daclatasvir dihydrochloride (Ph. Int.)

F. Dissolve 20 mg of the test substance in 20 mL methanol R; the solution yields reaction A described under [2.1 General identification tests](#) as characteristic of chlorides.

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

**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 1; determine the heavy metals content according to method A; not more than 20 µg/g.

**Water.** Determine as described under [2.8 Determination of water by the Karl Fischer method](#), method A, using 0.2000 g of the substance; the water content is not more than 10 mg/g.

**pH value.** pH of a 10 mg/mL solution, 2.5–3.5

**Impurity A (daclatasvir enantiomer).** Carry out test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (15 cm × 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded cellulose *tris* (3,5-dichlorophenyl carbamate) (3 µm).<sup>1</sup> As mobile phase use a mixture of 30 volumes of 1.58 g per litre ammonium bicarbonate R in water and 70 volumes of acetonitrile R.

Operate at a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 320 nm. Maintain the column temperature at 40°C.

Prepare the following solutions in mobile phase. For solution (1) dissolve 25.0 mg of the test substance in 50.0 mL. For solution (2) dilute 5.0 mL of solution (1) to 100.0 mL. Dilute 2.0 mL of this solution to 100.0 mL. For solution (3) use a solution containing 0.01 mg daclatasvir impurity A and 0.01 mg daclatasvir dihydrochloride RS per mL.

Inject 10 µL of solution (3). The test is not valid unless the resolution factor between the peaks due to daclatasvir (retention time about 4.5 minutes) and impurity A (daclatasvir enantiomer) (relative retention of about 1.6) is at least 3.0.

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

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A (daclatasvir enantiomer) is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

**Related substances.** Carry out the test as described under [1.14.4 High-performance liquid chromatography](#).

Use the following conditions for gradient elution:

mobile phase A: 0.1% (v/v) solution of trifluoroacetic acid R;

mobile phase B: a mixture of 30 volumes of methanol R and 70 volumes of acetonitrile R.

<sup>1</sup> A Lux i-Cellulose-5 column or a Chiralpak IC-3 column were found suitable.

## Daclatasvir dihydrochloride (Ph. Int.)

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–1	80	20	Isocratic
1–25	80 to 55	20 to 45	Linear gradient
25–30	55 to 30	45 to 70	Linear gradient
30–35	30	70	Isocratic
35–37	30 to 80	70 to 20	Return to initial composition
37–45	80	20	Re-equilibration

Operate at a flow rate of 1.0 mL/minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 304 nm. Maintain the column at a temperature of 40°C.

Prepare the following solutions using as diluent a mixture of 80 volumes of mobile phase A and 20 volumes of mobile phase B. For solution (1) dissolve 25.0 mg of the substance to be examined and dilute to 50.0 mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 5.0 mL of this solution to 50.0 mL. For solution (3) use a solution containing 0.5 mg of daclatasvir for peak identification RS (containing daclatasvir and the impurities B, D, F, G, H and I) per mL.

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

Use the chromatogram obtained with solution (3) and the chromatogram supplied with daclatasvir for peak identification RS to identify the peaks due to the impurities B, D, F, G, H and I in the chromatogram obtained with solution (1). The test is not valid unless the peak-to-valley ration ( $H_p/H_v$ ) is at least 20, where  $H_p$  is the height above the extrapolated baseline of the peak due to the co-eluting impurities B and C and  $H_v$  is the height above the extrapolated baseline at the lowest point of the curve separation the peak due to daclatasvir from the peak due to the co-eluting impurities B and C. The impurities, if present, are eluted at the following relative retentions with reference to daclatasvir (retention time about 17 minutes): impurity I about 0.21; impurity H about 0.62; impurity G about 0.76; impurities B and C about 1.12; impurity E about 1.16; impurity D about 1.22; impurity J about 1.39; impurity K about 1.66; and impurity F about 1.82.

In the chromatogram obtained with solution (1):

- the sum of the areas of any peak corresponding to impurities B and C (impurities B and C may co-elute) is not greater than 1.5 times the area of the peak due to daclatasvir obtained with solution (2) (0.15%);
- the area of any peak corresponding to impurities I, H, G, D or F is not greater than 1.5 times the area of the peak due to daclatasvir obtained with solution (2) (0.15%);
- the area of any other impurity peak is not greater than the area of the peak due to daclatasvir obtained with solution (2) (0.10%);
- the sum of the areas of all impurity peaks is not greater than 10 times the area of the principal peak obtained with solution (2) (1.0%). Disregard any peak with an area less than 0.5 times the area of the peak due to daclatasvir obtained with solution (2) (0.05%).

## Daclatasvir dihydrochloride (Ph. Int.)

**Assay**

- Either method A or method B may be applied.
- A. Carry out test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (15 cm x 4.6 mm) packed with base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3.5 µm).<sup>2</sup>

Use the following conditions for gradient elution:

mobile phase A: 0.1 % (v/v) solution of trifluoroacetic acid R;

mobile phase B: a mixture of 50 volumes of methanol R and 50 volumes of acetonitrile R.

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–1	70	30	Isocratic
1–13	70 to 60	30 to 40	Linear gradient
13–16	60 to 15	40 to 85	Linear gradient
16–18	15	85	Isocratic
18–20	15 to 70	85 to 30	Return to initial composition
20–25	70	30	Re-equilibration

Operate at a flow rate of 1.0 mL/minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 304 nm. Maintain the column at a temperature of 40°C.

Prepare the following solutions using as diluent a mixture of 70 volumes of mobile phase A and 30 volumes of mobile phase B.

For solution (1) dissolve 25.0 mg of the substance to be examined and dilute to 50.0 mL. Dilute 10.0 mL of this solution to 50.0 mL. For solution (2) dissolve 25.0 mg of daclatasvir dihydrochloride RS and dilute to 50.0 mL. Dilute 10.0 mL of this solution to 50.0 mL.

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

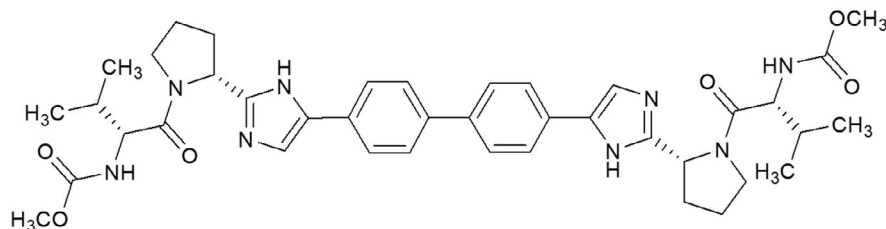
Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of daclatasvir dihydrochloride ( $C_{40}H_{50}N_8O_6 \cdot 2HCl$ ) using the declared content of  $C_{40}H_{50}N_8O_6 \cdot 2HCl$  in daclatasvir dihydrochloride RS.

- B. Dissolve about 0.3 g, accurately weighed, in 5 mL water and add 20 mL of ethanol (~750 g/L) TS. Titrate with sodium hydroxide (0.1 mol/L) VS, determining the end-point potentiometrically. Each mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 40.59 mg of  $C_{40}H_{50}N_8O_6 \cdot 2HCl$ .

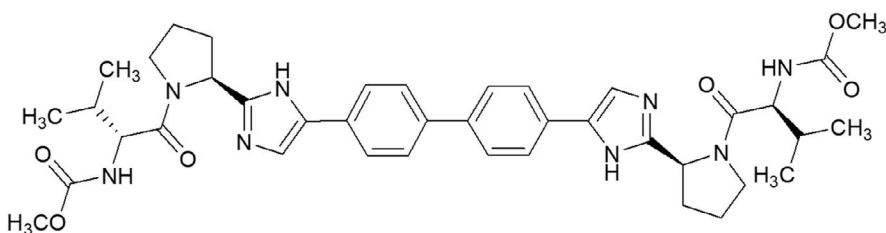
<sup>2</sup> An XBridge C18 column or a Zorbax SB C18 column were found suitable.

## Daclatasvir dihydrochloride (Ph. Int.)

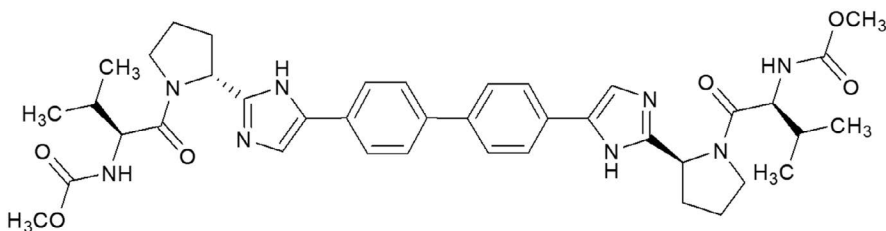
## Impurities



- A. Methyl *N*-[(2*R*)-1-[(2*R*)-2-[5-[4-[4'-[2-[(2*R*)-1-[(2*R*)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1*H*-imidazol-5-yl]phenyl]phenyl]-1*H*-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (daclatasvir enantiomer) (synthesis-related impurity)

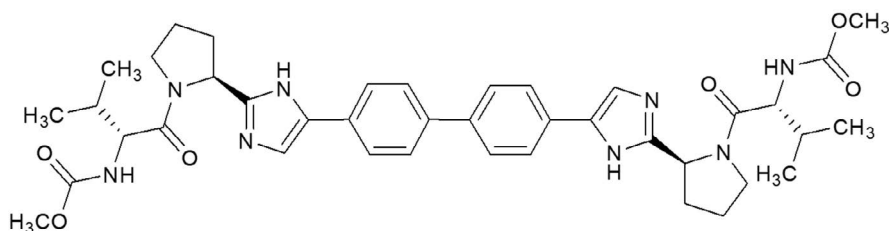


- B. Methyl *N*-[(2*R*)-1-[(2*S*)-2-[5-[4-[4'-[2-[(2*S*)-1-[(2*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1*H*-imidazol-5-yl]phenyl]phenyl]-1*H*-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (RSSS diastereomer) (synthesis-related impurity)

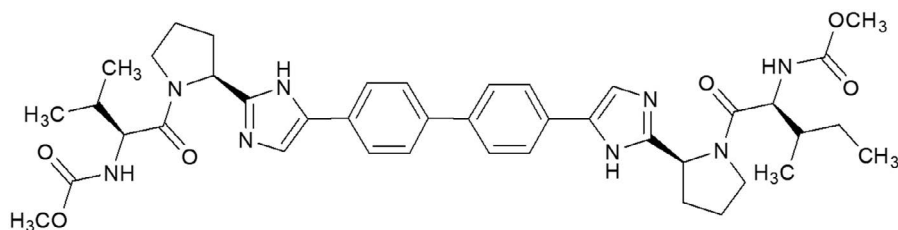


- C. Methyl *N*-[(2*S*)-1-[(2*R*)-2-[5-[4-[4'-[2-[(2*S*)-1-[(2*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1*H*-imidazol-5-yl]phenyl]phenyl]-1*H*-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (SRSS diastereomer) (synthesis-related impurity)

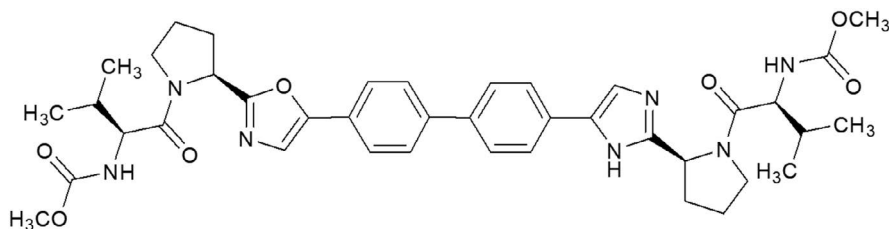
## Daclatasvir dihydrochloride (Ph. Int.)



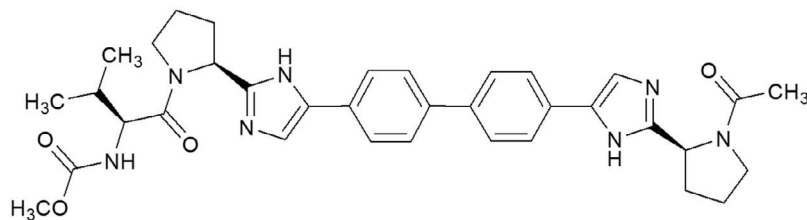
- D. Methyl *N*-[(2*R*)-1-[(2*S*)-2-[5-[4-[4'-[2-[(2*S*)-1-[(2*R*)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1*H*-imidazol-5-yl]phenyl]phenyl]-1*H*-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (RSSR diastereomer) (synthesis-related impurity)



- E. Methyl *N*-[(2*S*)-1-[(2*S*)-2-[5-[4-[4'-[2-[(2*S*)-1-[(2*S*)-2-(methoxycarbonylamino)-3-methylbutanoyl]pyrrolidin-2-yl]-1*H*-imidazol-5-yl]phenyl]phenyl]-1*H*-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl]carbamate (synthesis-related impurity)



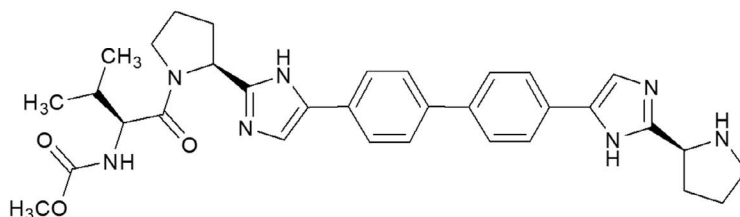
- F. Methyl [(2*S*)-1-[(2*S*)-2-[5-(4'-{2-[(2*S*)-1-[(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl]pyrrolidin-2-yl]-1,3-oxazol-5-yl}biphenyl-4-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (synthesis-related impurity)



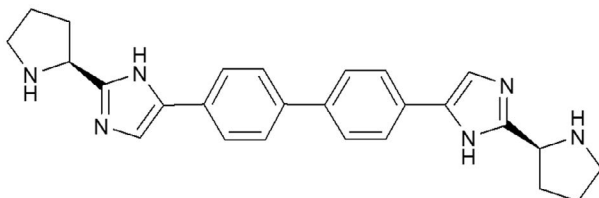
- G. Methyl [(2*S*)-1-[(2*S*)-2-[5-(4'-{2-(2*S*)-1-acetylpyrrolidin-2-yl]-1*H*-imidazol-5-yl}biphenyl-4-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl]carbamate (synthesis-related impurity)



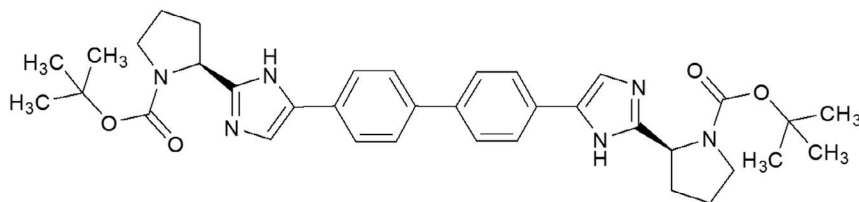
## Daclatasvir dihydrochloride (Ph. Int.)



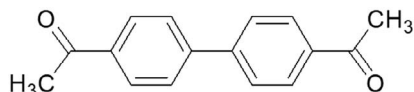
- H. Methyl((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate (synthesis-related impurity)



- I. 5,5'-[1,1'-Biphenyl]-4,4'-diylbis[2-(2S)-2-pyrrolidinyl-1H-imidazole] (synthesis-related impurity)



- J. (2S,2'S)-2,2'-([1,1'-biphenyl]-4,4'-diyl-di-1H-imidazole-5,2'-diyl)bis-1-pyrrolidinecarboxylic acid 1,1'-bis(1,1-dimethylethyl) ester (synthesis-related impurity)



- K. 4,4'-Diacetylbiphenyl (synthesis-related impurity)

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## Daclatasvir tablets (*Daclatasviri compressi*)

**This is a draft proposal of a monograph for *The International Pharmacopoeia* (Working document QAS/18.763, May 2018). The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).**

**Note from the Secretariat.** *The monograph on Daclatasvir tablets is proposed for inclusion in The International Pharmacopoeia.*

*The methods and specifications were drafted based on information provided by manufacturers, found in the scientific literature and on laboratory investigations.*

*Being the first public specification, this monograph is expected to play an important role in ensuring access to safe, effective and quality-assured daclatasvir tablets worldwide. All manufacturers of these products are therefore invited to provide their feedback to the Secretariat of The International Pharmacopoeia to help ensure that this proposed monograph adequately controls the daclatasvir tablets they manufacture.]*

**Category.** Antiviral (Nonstructural protein 5A inhibitor)

**Storage.** Daclatasvir tablets should be kept in a well-closed container.

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

**Additional information.** Strength in the current WHO Model List of Essential Medicines (EML): 30 mg and 60 mg daclatasvir.

### Requirements

Comply with the monograph for [Tablets](#).

**Definition.** Daclatasvir tablets contain Daclatasvir dihydrochloride. They contain not less than 90.0% and not more than 110.0% of the amount of daclatasvir ( $C_{40}H_{50}N_8O_6$ ) stated on the label.

### Identity tests

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

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

- A.1. Carry out test as described under [1.14.1 Thin-layer chromatography](#) using silica gel R6 or similar as the coating substance and a mixture of 77 volumes of ethyl acetate R, 15 volumes of methanol R and 8 volumes of water R as the mobile phase. Apply separately to the plate 2  $\mu$ L of each of the following 2 solutions. For solution (A) shake a quantity of the powdered tablets containing 50 mg of daclatasvir with 5 mL of methanol R and filter. For solution (B) use a solution containing 11 mg of daclatasvir dihydrochloride RS per mL methanol R. After removing the plate from the

**Daclatasvir tablets (Ph. Int.)**

chromatographic chamber allow it to dry in air or in a current of cool air. Examine the chromatogram in ultraviolet light (365 nm).

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

A.2. Carry out the test as described under [1.14.1 Thin-layer chromatography](#) using the conditions described above under text A.1. After drying the plate spray with basic potassium permanganate (5 g/L) TS. Examine the chromatogram in daylight.

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

- B. Carry out the test as described under [1.14.4 High-performance liquid chromatography](#) using the conditions and solutions 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 daclatasvir in the chromatogram obtained with solution (2).
- C. To a quantity of powdered tablets containing the equivalent of 10 mg daclatasvir add 40 mL methanol R, sonicate for 5 minutes, allow to cool to room temperature, dilute to 50 mL and filter. Dilute 1 mL of the filtrate to 20 mL with methanol R. The absorption spectrum ([1.6](#)) of the resulting solution, when observed between 230 nm and 400 nm, exhibits one maximum at 314 nm.

**Dissolution.** Carry out the test as described under [5.5 Dissolution test for solid oral dosage forms](#) using as the dissolution medium 500 mL of dissolution buffer pH 6.8 and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of 10 mL of the medium through an in-line filter. Allow the filtered sample to cool down to room temperature.

If necessary, dilute a suitable volume of the filtrate with dissolution medium to obtain a solution containing 0.06 mg of daclatasvir per mL. Measure the absorbance ([1.6](#)) of a 1 cm layer of the resulting solution at the maximum at about 314 nm, using the dissolution buffer as the blank. Measure at the same time and under the same conditions the absorbance of a suitable solution of daclatasvir dihydrochloride RS in the dissolution buffer.

For each of the tablets tested calculate the amount of daclatasvir ( $C_{40}H_{50}N_8O_6$ ) in the medium. Each mg of daclatasvir dihydrochloride is equivalent to 0.910 mg of daclatasvir.

Evaluate the results as described under [5.5 Dissolution test for solid oral dosage forms](#), Acceptance criteria. The amount of daclatasvir in solution for each tablet is not less than 75% (Q) of the amount declared on the label.

**Related substances.** Carry out test as described under [1.14.4 High-performance liquid chromatography](#).

Use the following conditions for gradient elution:

mobile phase A: 0.1% (v/v) solution of trifluoroacetic acid;

mobile phase B: a mixture of 30 volumes of methanol R and 70 volumes of acetonitrile R.

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Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–1	80	20	Isocratic
1–25	80 to 55	20 to 45	Linear gradient
25–30	55 to 30	45 to 70	Linear gradient
30–35	30	70	Isocratic
35–37	30 to 80	70 to 20	Return to initial composition
37–45	80	20	Re-equilibration

Prepare the following solutions using as diluent a mixture of 80 volumes of mobile phase A and 20 volumes of mobile phase B.

For solution (1) transfer a quantity of the powdered tablets containing the equivalent of 25.0 mg of daclatasvir to a 40 mL volumetric flask. Add about 30 mL diluent and sonicate for 5 minutes, cool to room temperature and make up to the volume with the diluent and filter. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 5.0 mL to this solution to 50.0 mL. For solution (3) use a solution containing 0.5 mg of daclatasvir for peak identification RS (containing daclatasvir and the impurities B, D, F, G, H and I) per mL.

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

Use the chromatogram supplied with daclatasvir for peak identification to identify the peaks due to the impurities H and G in the chromatogram obtained with solution (3). The test is not valid unless the peak-to-valley ration ( $H_p/H_v$ ) is at least 20, where  $H_p$  is the height above the extrapolated baseline of the peak due to the co-eluting impurities B and C and  $H_v$  is the height above the extrapolated baseline at the lowest point of the curve separation the peak due to daclatasvir from the peak due to the co-eluting impurities B and C.

In the chromatogram obtained with solution (1):

- the area of any impurity peak is not greater than 2 times the area of the peak due to daclatasvir in the chromatogram obtained with solution (2) (0.2%);
- the sum of all areas of all impurity peaks is not greater than 15 times the area of the peak due to daclatasvir obtained with solution (2) (1.5%). Disregard any peak with an area less than the area of the peak due to daclatasvir obtained with solution (2) (0.1%).

**Assay.** Carry out test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (15 cm x 4.6 mm) packed with base-deactivated particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3.5 µm).<sup>1</sup>

Use the following conditions for gradient elution:

mobile phase A: 0.1% (v/v) solution of trifluoroacetic acid;

mobile phase B: a mixture of 50 volumes of methanol R and 50 volumes of acetonitrile R.

<sup>1</sup> An XBridge C18 column or a Zorbax SB C18 column were found suitable.

**Daclatasvir tablets (Ph. Int.)**

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–1	70	30	Isocratic
1 - 13	70 to 60	30 to 40	Linear gradient
13–16	60 to 15	40 to 85	Linear gradient
16–18	15	85	Isocratic
18–20	15 to 70	85 to 30	Return to initial composition
20–25	70	30	Re-equilibration

Operate at a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 304 nm. Maintain the column temperature at 40°C.

Prepare the following solutions using as diluent a mixture of 70 volumes of mobile phase A and 30 volumes of mobile phase B.

For solution (1) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets containing 100.0 mg of daclatasvir to a 100 mL volumetric flask. Add about 60 mL of diluent and sonicate for 5 minutes, cool to room temperature and make up to volume with diluent. Filter and dilute 5.0 mL of the filtrate to 50.0 mL. For solution (2) dissolve 55.0 mg of daclatasvir dihydrochloride RS and dilute to 50.0 mL. Dilute 5.0 mL of this solution to 50.0 mL.

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

Measure the areas of the peak responses corresponding to daclatasvir obtained in the chromatograms from solutions (1) and (2) and calculate the percentage content of daclatasvir ( $C_{40}H_{50}N_8O_6$ ) in the tablets using the declared content of  $C_{40}H_{50}N_8O_6 \cdot 2HCl$  in daclatasvir dihydrochloride RS. Each mg of daclatasvir dihydrochloride is equivalent to 0.910 mg of daclatasvir.

**Impurities**

The impurities limited by the requirements of this monograph include those listed in the monograph on Daclatasvir dihydrochloride.

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## Polymorphism

**This is a draft proposal of a chapter for *The International Pharmacopoeia* (Working document QAS/17.716/Rev.1, May 2018). The draft has been revised based on the comments received during the public consultation held in July–September 2017. The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).**

*[Note from the Secretariat. It is proposed to publish the following chapter on Polymorphism in the Supplementary Information section under “Notes for guidance”.]*

### Introduction and terminology

The aim of this chapter is to provide a brief overview of:

- the terminology associated with crystal polymorphism;
- some analytical techniques commonly used to characterise polymorphs;
- the relevance of polymorphism for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs); and
- the control strategies for polymorphism employed by *The International Pharmacopoeia*.

APIs and excipients, in the solid phase, can be classified as either crystalline or non-crystalline solids or a mixture thereof. A crystalline structure implies that the structural units (*i.e.* the unit cells) are repeated in a long range order. The atoms and/or molecules of an amorphous solid, however, are arranged in a non-ordered, random system, such as in the liquid state, and do not possess a distinguishable crystal lattice. Amorphous solids are classified as non-crystalline solids.

Variation in the crystallization conditions (temperature, pressure, solvent, concentration, rate of crystallization, seeding of the crystallization medium, presence and concentration of impurities, etc.) may cause the formation of different forms.

When the crystalline structure of the same chemical compound (and atomic formula) exhibit two or more patterns of the repeated unit cells, these crystalline structures are called *polymorphs* and the phenomena is referred to as *polymorphism*. The difference in internal crystal structure could be attributed to differences in molecule packing arrangements and/or different molecular conformations. When a chemical element (e.g. sulfur) exists in different crystalline forms, it is referred to as *allotropy*, not polymorphism (1). Due to the identical chemical composition of the polymorphic substance it will have the same chemical behaviour in solution, irrespective in the form in which it is presented.

Crystals of the same chemical compound with the same internal structure may exhibit different external shapes or *crystal habits*.

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### Polymorphism (Ph. Int.)

*Solvates* are crystal forms containing stoichiometric or non-stoichiometric quantities of a solvent. When the solvent incorporated into the crystal structure of the compound is water, the molecular adduct formed is referred to as a *hydrate*. Solvation and hydration products are also sometimes referred to as *pseudopolymorphs*. (2, 3, 4) However, the term “pseudopolymorphism” is ambiguous because of its use in different circumstances. It is therefore preferable to use only the terms “solvates” and “hydrates”.

Occasionally a compound of a given hydration/solvation state may crystallize into more than one crystalline form; an example of such a compound is nitrofurantoin. (5) Nitrofurantoin can be crystallized as two monohydrate forms (Forms I and II) and two anhydrous forms (designated polymorphs  $\alpha$  and  $\beta$ ). (5)

Crystal forms are said to be *isostructural* when they have the same overall crystal packing. Solvates, which have the same overall crystal packing, but differ only in the solvents included in their crystal structures, are termed *isostructural solvates*, e.g. hydrate and isopropanolate of hexakis(2,3,6-tri-O-acetyl)- $\alpha$ -cyclodextrin. (6)

The term *desolvated solvate* (which includes hydrates) has been used to classify a compound that was originally crystallized as a solvate but when the incorporated solvent is removed the crystal lattice of the solvated and desolvated crystal lattices show no or only relatively small differences. (4) for example, desolvated monohydrate of terazosin HCl. (7)

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

Traditionally polymorphic forms of an API are classified as either crystalline, amorphous or solvate and hydrate forms. *Co-crystals* are crystalline materials composed of two or more different molecules, typically an API and co-crystal formers (“conformers”) within the same crystal lattice that are associated by nonionic and noncovalent bonds. An example of a co-crystal is fluoxetine HCl/succinic acid co-crystal. (8) Co-crystals are thus more similar to solvates, in that both contain more than one component in the lattice. However, for co-crystals the conformer is non-volatile. (3)

Pharmaceutical co-crystals have gained considerable attention as alternative forms in an attempt to enhance the bioavailability, stability and processability of the API in the manufacturing process. Another advantage of co-crystals is that they generate a diverse array of solid state forms for APIs that lack ionisable functional groups, which is a prerequisite for salt formation. (3) Guidance and reflection papers on the use and classification of pharmaceutical co-crystals have been published. (3, 9)

### Characterization and thermodynamic stability of solid forms

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



**Table 1. Examples of physical properties that may differ among different forms**

<p><b>1. Packing properties</b></p> <ul style="list-style-type: none"> <li>a. Molar volume and density</li> <li>b. Refractive index</li> <li>c. Conductivity (electrical and thermal)</li> <li>d. Hygroscopicity</li> </ul> <p><b>2. Thermodynamic properties</b></p> <ul style="list-style-type: none"> <li>a. Melting and sublimation temperatures</li> <li>b. Internal energy (<i>i.e.</i> structural energy)</li> <li>c. Enthalpy (<i>i.e.</i> heat content)</li> <li>d. Heat capacity</li> <li>e. Entropy</li> <li>f. Free energy and chemical potential</li> <li>g. Thermodynamic activity</li> <li>h. Vapour pressure</li> <li>i. Solubility</li> </ul>	<p><b>3. Spectroscopic properties</b></p> <ul style="list-style-type: none"> <li>a. Electronic state transitions</li> <li>b. Vibrational state transitions</li> <li>c. Nuclear spin state transitions</li> </ul> <p><b>4. Kinetic properties</b></p> <ul style="list-style-type: none"> <li>a. Dissolution rate</li> <li>b. Rates of solid state reactions</li> <li>c. Stability</li> </ul> <p><b>5. Surface properties</b></p> <ul style="list-style-type: none"> <li>a. Surface-free energy</li> <li>b. Interfacial tensions</li> <li>c. Habit (<i>i.e.</i> shape)</li> </ul> <p><b>6. Mechanical properties</b></p> <ul style="list-style-type: none"> <li>a. Hardness</li> <li>b. Tensile strength</li> <li>c. Compatibility, tableting</li> <li>d. Handling and flow</li> </ul>
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*Table 2* summarizes some of the most commonly used techniques to study and/or classify different forms. These techniques are often complementary and it is indispensable to use several of them. Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. X-ray powder diffraction can also be used to provide unequivocal proof of polymorphism.<sup>(10)</sup>

Any technique(s) chosen to confirm the identity of the specific form(s) must be proven to be suitably specific for the identification of the desired form(s). Care must be taken in choosing the appropriate sample preparation technique, as heat generation or exposure to elevated pressure may trigger conversion between different forms.

**Table 2. Examples of some techniques that may be used to study and/or classify different crystalline forms**

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

\* Methods currently employed by *The International Pharmacopoeia*

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### Polymorphism (Ph. Int.)

Using suitable analytical techniques, the thermodynamic stability of the forms should be investigated. The form with the lowest free energy is the most thermodynamically stable at a given temperature and pressure. The other forms are said to be in a metastable state. At normal temperature and pressure, a metastable form may remain unchanged or may change to a thermodynamically more stable form. In general the more stable the form the less soluble it is. Conversion to a thermodynamically more stable form, may cause changes in some of the physical properties (see [Table 1](#)) of the compound that may result in changes to other critical properties such as bioavailability, manufacturability (also referred to as processability), etc.

If there are several crystalline forms one form is thermodynamically more stable at a given temperature and pressure. A given crystalline form may constitute a phase that can reach equilibrium with other solid phases and with the liquid and gas phases.

If each crystalline form is the more stable within a given temperature range the change from one form to another is reversible and is said to be *enantiotropic*. The change from one phase to another is a univariate equilibrium so that at a given pressure this state is characterized by a transition temperature. However, if only one of the forms is stable over the entire temperature range, the change is irreversible or *monotropic*.<sup>(11)</sup>

### Relevance of polymorphism for APIs and FPPs

Polymorphism of APIs and excipients are of interest as they may affect bioavailability, toxicity and processability. Also the thermodynamic stability of the form included in the FPP is considered important as environmental conditions may compromise the stability thereof. For formulations where the API is dissolved, attention has to be paid to supersaturation with regards to different forms. A formulation might not be supersaturated regarding a metastable polymorph but supersaturated with regards to the thermodynamically stable polymorph. Control of the form by the manufacturer may be required during the processing of APIs and excipients and during the manufacturing of a dosage form to ensure the correct physical characteristics thereof. The control of a specific form is especially critical in the areas where the bioavailability, stability or processability are directly impacted.<sup>(4)</sup>

The form of a readily soluble API that is incorporated into a solution, for example, an injection, an oral solution or eye drops, is normally non-critical (an exception to this statement might be if the concentration of the solution is such that it is close to the limit of solubility of one of the possible polymorphs – as mentioned above). Similarly, if an API is processed during the manufacturing process to obtain an amorphous form (e.g. hot melt extrusion, spray-dried dispersion, etc.), the original form is considered non-critical, as long as the processability is not influenced.

The form may be critical when the material is included in a solid dosage form or as a suspension in a liquid dosage form. In such cases the characteristics of the different polymorphs may affect the bioavailability or dissolution of the material. The polymorphic form of a biopharmaceutical classification system (BCS) class I or III API in a solid oral dosage form is normally non-critical in terms of dissolution rate or bioavailability as by definition it would be readily soluble, but confirmation thereof by the manufacturer, is recommended. The ICH Harmonised Tripartite Guideline on Specifications: Test procedures and acceptance criteria for

new drug substances and new drug products: Chemical substances Q6A, provides guidance on when and how polymorphic forms should be monitored.<sup>(4)</sup>

The inclusion of potentially harmful solvents in the crystal lattice, which may render APIs or excipients to be toxic or harmful to patients (*i.e.* solvates), should also be suitably regulated and monitored by the manufacturer.

### Polymorphism in *The International Pharmacopoeia*

Where a monograph indicates that a compound shows polymorphism this may be true crystal polymorphism, occurrence of solvates or occurrence of the amorphous form.

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

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

The control of forms specified in *The International Pharmacopoeia* may be achieved by:

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

When the infrared identification test is able to detect differences in forms for a specific compound (*i.e.* polymorphism may be present for this compound), but the control of a specific form is not required by the monograph, the user may be instructed to:

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

Whenever the choice of a specific form is critical with regard to bioavailability and/or stability, the method of the manufacturer of the product must be validated to consistently yield the desired polymorph in the final product at release and over its shelf life. The monograph will include a statement under the heading “Manufacturing” to draw attention to the control of a specified form during manufacturing where control is known to be critical, for example, carbamazepine oral suspension.

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**Polymorphism (Ph. Int.)**

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

**References**

- 1 Gaskell, DR. 2005. Allotropy and Polymorphism. Reference Module in Materials Science and Materials Engineering. Encyclopedia of Condensed Matter Physics, 8–17.
- 2 Brittain, HG. 2007. Polymorphism and solvatomorphism 2005. *Journal of Pharmaceutical Sciences*, 96(4):705–728.
- 3 US Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research. 2013. Guidance to industry: Regulatory classification of pharmaceutical co-crystals.
- 4 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 1999. ICH Q6A – Specifications: The procedures and acceptance criteria for new drug substances and new drug products: Chemical substances.
- 5 Caira, M, Pienaar, EW, Lötter, AP. 2006. Polymorphism and pseudopolymorphism of the antibacterial nitrofurantoin. *Molecular Crystals and Liquid Crystals*, 179(1):241-264.
- 6 Bettinetti, G., Sorrenti, M., Catenacci, L., Ferrari, F. & Rossi, S. Bettinetti, G, et al. 2006. Polymorphism, pseudopolymorphism, and amorphism of peracetylated  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrins. *Journal of Pharmaceutical and Biomedical Analysis*, 41:1205-1211.
- 7 Bauer, J, et al. 2006. Identification, preparation and characterization of several polymorphs and solvates of terazosin hydrochloride. *Journal of Pharmaceutical Sciences*, 95(4):917-928.
- 8 Peterson, ML, et al. 2006. Expanding the scope of crystal form evaluation in pharmaceutical science. *Journal of Pharmaceutical Sciences*, 9(3):317-326.
- 9 European Medicines Agency. 2015. Reflection paper on the use of cocrystals of active substances in medicinal products.
- 10 US Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research. 2007. Guidance to industry: ANDAs: Pharmaceutical Solid Polymorphism. Chemistry, Manufacturing and Controls Information.
- 11 British Pharmacopoeia Commission. 2017. SC I B. Polymorphism. In: British Pharmacopoeia Commission. British Pharmacopoeia 2017. Supplementary chapter. London: TSO.

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**WHO medicines quality guidelines**

## Inquiry regarding production of water for injections

**Working document QAS/18.764 (March 2018), reproduced below, relates to a public inquiry on whether to revise the WHO specifications and good manufacturing practices (GMP) for the production of water for injections. The working document with line numbers is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).**

### 1. Background

Several pharmacopoeias, including the European Pharmacopoeia, during the past years and months adopted revised monographs on water for injections (WFI) allowing production by non-distillation technologies.

Up until now, the production of WFI had been limited to distillation only in many countries. The monograph revisions in the context of several pharmacopoeias were the result of extensive consultations with stakeholders. They newly allow for production of WFI by a purification process equivalent to distillation such as reverse osmosis, coupled with appropriate techniques.

The Japanese Pharmacopoeia and the US Pharmacopoeia, for example, allow for production of WFI by distillation or a purification process proven to be equal or superior to distillation, and by distillation or reverse osmosis followed by ultrafiltration, respectively.

In the European context, EDQM conducted a survey in 2010 to gather data on the use of non-distillation technologies for producing WFI and organized an expert workshop in March 2011. The revised monograph in the European Pharmacopoeia foresees that the use of non-distillation technologies for the production of WFI requires that notice is given to the supervisory authority of the manufacturer before implementation.

Any non-distillation technology for producing WFI should be equivalent in quality to that produced by distillation, where equivalence in quality does not simply mean compliance with a specification but also takes into account the robustness of the production method. This is why the ongoing general revision of Annex 1 “Manufacture of sterile medicinal products” to the European Union good manufacturing practices (GMP) guidelines will include new guidance on production methods for WFI. In order to ensure the necessary guidance is available for the newly revised European monograph implementation, a question-and-answer (Q&A) document was prepared by the GMP/GMDP Inspectors Working Group of the European Medicines Agency.

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Inquiry regarding production of water for injections

## 2. WHO context

At an informal WHO consultation on good practices for health products manufacture and inspection held in April 2017, it was noted that new technologies were being adopted for the manufacture of WFI internationally, as outlined above. The monograph on “**Water** for injections” included in *The International Pharmacopoeia* and the GMP for water describe a distillation process only when used as WFI, whereas other technologies, such as reverse osmosis, have been included in other pharmacopoeias.

This was reported to the 52nd WHO Expert Committee on Specifications for Pharmaceutical Preparations. The Expert Committee members noted the report and recommended that the WHO Secretariat should collect feedback on whether to revise the WHO specifications and GMP in relation to the production of WFI.

Within the context of the WHO publications the following contain information on the production of WFI by distillation only:

- WHO good manufacturing practices: water for pharmaceutical use (WHO Technical Report Series, No. 970, Annex 2, 2012);
- Monograph on Water for injections in *The International Pharmacopoeia*: <http://apps.who.int/phint/2017/index.html#p/home>.

In light of the above, feedback is being sought on whether the WHO specifications and GMP text(s):

- should be revised in relation to the production of WFI allowing other purification processes as well,
  - and if yes, if details on additional requirements should be added,
  - and if yes, which additional requirements should be added.

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## Proposal for revision of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce

**Working document QAS/18.768 (April 2018) relates to a proposed revision of the WHO Certification Scheme, a voluntary agreement among Member States to provide assurance about the quality of pharmaceutical products moving in international commerce. The working document with line numbers and tracked changes is available for comment at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects).**

### 1. Introduction

The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (the “Scheme”) is an international voluntary agreement to provide assurance, to countries participating in the Scheme, about the quality of pharmaceutical products moving in international commerce. The primary document of the Scheme is the certificate of a pharmaceutical product (CPP).

The fifty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSP) in 2017 was informed about the current situation of the Scheme, including the fact that the forty-third Expert Committee in 2008 had recommended that “the *WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce* should be revised” in line with recent developments. The Expert Committee in 2017 recommended that the “WHO Secretariat should prepare a proposal for revision of the Scheme for public consultation”.

The objective of this working document is to compile key issues on the Scheme and provide a proposed revision of the Scheme for consideration during the upcoming fifty-third ECSP meeting in 2018.

### 2. Background

The Scheme has been in operation since 1969 (World Health Assembly resolution WHA 22.50) and was amended in 1975 (WHA 28.65), 1988 (WHA 41.18), 1992 (WHA 45.29) and 1997 (WHA 50.3) (1–5). The current Scheme provides the following three types of certificate:

- CPP;
- statement of the licensing status of pharmaceutical product;
- batch certificate.

In 2007, the forty-second ECSP discussed and identified a number of perceived problems with the operation of the Scheme (6).

In 2008, a WHO consultation was held to make recommendations for consideration during the forty-third ECSP, taking account of the WHO working document QAS/07.240 which contains key issues and possible action (7). The forty-third ECSP in 2008 discussed the report of the consultation (working document QAS/08.279) (8). In light of the changing environment, including the rapid globalization of the pharmaceutical manufacturing sector, coupled with changes in the make-up of both the regulators and the groups involved in procurement, the

Proposal for revision of the WHO Certification Scheme

forty-third ECSPP endorsed the following recommendations (9):

- “1. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce should be revised;
- 2. The proposal for revision of the Scheme and modification of the guidelines should be discussed by the relevant WHO Governing Bodies – the Executive Board and the World Health Assembly – and in consultation with WHO’s Legal Counsel.
- 3. In the interim a question and answer (Q&A) paper should be prepared on the function of the Scheme.”

Based on the above recommendation, as an interim measure, a Q&A document on the function of the Scheme was developed in 2010 and it was revised in 2015 (10, 11). However, the Scheme itself has not been revised since 1997.

In 2017, the fifty-second ECSPP recommended that the “WHO Secretariat should prepare a proposal for revision of the scheme for public consultation” (12).

The draft working document which includes the proposed revision of the Scheme was prepared by the WHO Secretariat and it will be discussed during an informal consultation planned to be held on 19 to 20 May 2018. In addition, the draft working document will be circulated, including to the Member States and other interested parties, for public consultation to prepare a

version of the working document for possible endorsement by the fifty-third ECSPP.

**3. Proposed revision of the Scheme**

Since the last revision of the Scheme in 1997 it has been discussed on various occasions and key issues and possible actions have been identified. These are roughly classified into the following two aspects:

- (a) issues related to the revision of the Scheme;
- (b) issues related to implementation/operational aspects of the Scheme.

The objective of this working document is to provide a proposed revision of the scheme for consideration [endorsement/adoption] during the upcoming fifty-third ECSPP. Therefore, possible action related to implementation and operational aspects of the Scheme (e.g. promotion of the Scheme, making use of IT) would be considered after adoption of the revision of the Scheme.

**3.1 Summary of key issues and proposed actions related to the revision of the Scheme**

The table below outlines key issues and possible actions. These were prepared mainly based on the report of the forty-third ECSPP and on working documents QAS/07.240 and QAS/08.279 and the Q&A document<sup>1</sup> as well as comments from the Member States and interested parties during public consultation (6, 7, 9, 12).

<sup>1</sup> Q16 is “What are the main problem encountered in the application of the Scheme”

Key issues	Proposed actions
a The Scheme is formally at present directed to individual Member States, whereas regulatory and procurement groupings of multistate organizations also need to be able to operate within the Scheme; this applies to both issuing and receiving parties	The wordings in the Scheme should be changed so that regional organizations such as the European Union can formally participate in the Scheme  <i>[Note from Secretariat: Member State(s)] =&gt; “Member State(s) and/or regional authority(ies)”.]</i>

(Continued)



## Proposal for revision of the WHO Certification Scheme

*(Continued)*

Key issues	Proposed actions
b The list of competent authorities is out of date; details of some authorities have changed. The current list of countries that participate in the Scheme in its present form is not readily available	Memberships as “certificate-issuing” countries should be renewed every five years <b>[Note from Secretariat: Added new para. as section 2.5; See below for more detail.]</b> Member States should inform any update of the name and address of competent authorities to the WHO secretariat <b>[Note from Secretariat: Added new paragraph as section 2.7.]</b>
c Exporting countries that do not fulfil the prerequisites required by the Scheme issue certificates to support export	Memberships as “certificate -issuing” countries should be renewed every five years. Member States intending to continue to participate in the Scheme as “certificate-issuing” countries should resubmit notification to the Director-General of the World Health Organization (WHO) in the same way as section 2.1 <b>[Note from Secretariat: Added new paragraph as section 2.5.]</b> Member States intending to participate in the Scheme as certificate--issuing countries should declare that the competent authority meets the requirements in the notification to the WHO Director-General <b>[Note from Secretariat: Added new paragraph as section 2.4.]</b> In case that WHO does not receive the notification for renewal of membership for a long time period, the Director-General may delete such a Member State’s name from the participant list in consultation with the relevant Expert Committee <b>[Note from Secretariat: Added new paragraph as section 2.8.]</b>
d The CPP is no longer provided to substitute the full dossier quality safety and efficacy (QSE) review	CPPs should not be requested in countries that have the capability to conduct full QSE reviews <b>[Note from Secretariat: Added new paragraph as section 3.6.]</b>
e Information on who released the batch for marketing is not disclosed in certificates issued by exporting countries	The certificate should include batch release site information in the CPP as a new option (in section 2A.3, explanatory note 8 in model certificate of the guidelines) (“option c” will become the new “d” and a new “c” will be created) <b>[Note from Secretariat: Added new words in Appendix 1of the Annex.]</b>
f There have been cases in which forged certificates have been supplied to competent authorities of importing countries	Email address, telephone and fax numbers should be provided as contact information so that the requesting authority can request confirmation to the certifying authority countries easily <b>[Note from Secretariat: Added new words in section 2.4.]</b>
g Lead times of the certifying authorities can be very long, sometimes several months	Certifying authority should provide a certificate without undue delay <b>[Note from Secretariat: Added new paragraph as section 4.10.]</b>
h Importing countries require legalization of certificates, additional stamps, etc.	Unnecessary legalization should not be requested <b>[Note from Secretariat: Added new paragraph as section 4.7.]</b>

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 Proposal for revision of the WHO Certification Scheme

### 3.2 Proposed revision of the Scheme

The proposal for revision of the Scheme is attached as an annex. The amendments of the Scheme in the annex are presented in tracked-change mode. Moreover, it should be noted that this revision includes not only an amendment related to 3.1 in this working document but also editorial changes such as:

- updating some definitions in “Glossary and index” in conformity with latest version of relevant guidelines;
- replacing some words (e.g. “license” by “market authorization”).

### 4. Other issues related to operation of the Scheme

The table below outlines key issues not related to revision of the Scheme. As described in section 3 of this document, possible actions regarding implementation/operation of the Scheme (e.g. promotion of the Scheme, making use of IT) should be considered after adoption of the revision of the Scheme.

Key issues
a Countries not party to the Scheme issue certificates to support export of pharmaceutical products.
b Not all of certificate-issuing countries adhere to the WHO template
c Member States issue certificates for products not manufactured under their jurisdiction, e.g. for products not authorized for marketing in their countries or not manufactured in their country.
d Exporting countries issue other certificates such as free sale certificates.
e There are inconsistencies in listing the trade name of the product in the recipient country, if different from the certifying country.
f The way of applying for a CPP is not harmonized, with each certifying authority having its own system. (It would be helpful to work towards regional harmonization and a standard electronic submission.)

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### 5. References

- 1 World Health Assembly resolution WHA22.50 (1969).
- 2 World Health Assembly resolution WHA28.65 (1975).
- 3 World Health Assembly resolution WHA41.18 (1988).
- 4 World Health Assembly resolution WHA45.29 (1992).
- 5 World Health Assembly resolution WHA50.3 (1997).
- 6 Forty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations, Geneva (WHO Technical Report Series, No. 948 (2008)).
- 7 Proposal for improvement of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (working document QAS/07.240).
- 8 Draft report to the forty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations. Recommendations for improvement of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (QAS/08.279) (2008).
- 9 Forty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations, Geneva (WHO Technical Report Series, No. 953 (2009)).
- 10 WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce: Question and Answer (Q&A) (QAS/10.374, 2010)
- 11 WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce: Questions and Answers (Q & A) (WHO Drug Information Vol. 30, No. 3, 2016)
- 12 Fifty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 1010 (2018)).

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## Annex

**[Note from Secretariat:** In the *online document posted for comment*, the new text based on proposed action on the preceding pages is presented in tracked-change mode.]

### *Guidelines on the implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce*

#### 1. Provisions and objectives

1.1 A comprehensive system of quality assurance must be founded on a reliable system of marketing authorization and independent analysis of the finished pharmaceutical product, as well as upon assurance obtained through independent inspection that all manufacturing operations are carried out in conformity with accepted norms, referred to as good manufacturing practices (GMP).

1.2 In 1969, the Twenty-second World Health Assembly, by resolution WHA22.50, endorsed requirements for *Good Practices in the Manufacture and Quality Control of Drugs (1)* (referred to henceforth as “GMP as recommended by WHO”). These comprise internationally-recognized and respected standards that all Member States are urged to adopt and to apply. These requirements have since been revised several times.

1.3 These standards provide the basis for the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce (referred to henceforth as “the Scheme”) recommended initially in resolution WHA22.50 (1). The Scheme is an administrative instrument that requires each participating Member State or regional authority, upon application by a commercially interested party, to attest to the competent authority of another participating Member State or regional authority that:

- a specific product is authorized to be placed on the market within its jurisdiction or, if it is not thus authorized, the reason why that authorization has not been accorded;
- the plant in which it is produced is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP as recommended by the World Health Organization (WHO); and
- all submitted product information, including labelling, is currently authorized in the certifying country.

1.4 The Scheme, as amended in 1975 (2), 1988 (3), 1992 (4) and 1997 (5), by resolutions WHA28.65,

WHA41.18, WHA45.29 and WHA50.3, is applicable to finished dosage forms of pharmaceutical products intended for administration to human beings or to food-producing animals.

1.5 Provision for certification of active pharmaceutical ingredients (APIs) is also included within the scope of the Scheme. This will be the subject of separate guidelines and certificates.

#### 2. Membership

**[Note from Secretariat:** the new text in section 2 includes rearrangement of the order of paragraphs and such change is NOT presented in tracked-change mode in the *online document posted for comment*, except for the section number.]

2.1 Any Member State as well as regional authority that has legal right to control the regulation of pharmaceutical products are eligible to participate in the Scheme as a certifying member and/ or a requesting member if it complies with the requirements stipulated in section 2.2 or 2.3.

2.2 A Member State intending to become a certifying member should possess:

- an effective marketing authorization system, not only for pharmaceutical products, but also for the responsible manufacturers and distributors;
- GMP requirements, consonant with those recommended by WHO, to which all manufacturers of finished pharmaceutical products are required to conform;
- effective controls to monitor the quality of pharmaceutical products registered or manufactured within its country, including access to an independent quality control laboratory;
- a national pharmaceuticals inspectorate, operating as an arm of the national drug regulatory authority, and having the technical competence, experience and resources to assess whether GMP and other controls are being effectively implemented, and the legal power to conduct appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples;

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- administrative capacity to issue the required certificates, to institute inquiries in the case of complaint, and to notify expeditiously both WHO and the competent authority in any Member State known to have imported a specific product that is subsequently associated with a potentially serious quality defect or other hazard.
- 2.3 A regional authority intending to become a certifying member should possess by itself or through its legal framework:
- an effective marketing authorization system, not only for pharmaceutical products, but also for the responsible manufacturers and distributors;
  - GMP requirements, consonant with those recommended by WHO, to which all manufacturers of finished pharmaceutical products are required to conform;
  - effective controls to monitor the quality of pharmaceutical products registered or manufactured within its region, including access to an independent quality control laboratory;
  - a pharmaceuticals inspectorate, operating as an arm of the drug regulatory authority, and having the technical competence, experience and resources to assess whether GMP and other controls are being effectively implemented, and the legal power to conduct appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples;
  - administrative capacity to issue the required certificates, to institute inquiries in the case of complaint, and to notify expeditiously both WHO and the competent authority in any Member State and regional organization known to have imported a specific product that is subsequently associated with a potentially serious quality defect or other hazard.
- 2.4 Membership as a certifying member and/or requesting member can be applied by notifying in writing to the WHO Director-General of:
- its willingness to participate in the Scheme as a certifying member and/or a requesting member (Member States and regional authorities may participate only as a certifying member to control the import of pharmaceutical products and APIs);
  - any significant reservations it intends to observe relating to this participation;
  - the name and address (including email address, telephone and fax numbers) of its drug regulatory authority or other competent authority; and
  - declaration to comply with the requirements for a certifying member stipulated in section 2.2 or 2.3, if applicable.
- 2.5 A Member State and regional authority that has a membership of a certifying member should resubmit the notification in section 2.4 at least once every five years, in order to ensure that it continues to comply with the requirement stipulated in section 2.2 or 2.3 and that contact information keeps updated.
- 2.6 Consolidated list of information on the notification submitted by Member States and regional authorities in accordance with provision in sections 2.4, 2.5 and 2.7 will be available through WHO's official website (see also section 3.3).
- 2.7 A Member State and regional authority should inform WHO of any change of information notified to the WHO Director-General.
- 2.8 Membership as a certifying member may be disqualified by the Director-General after consultation with the ECSPP in the case that a Member State or regional authority would fail to resubmit a notification in accordance with provision in section 2.5 for a long period.
- 2.9 Each Member State and regional authority assumes the responsibility to determine, through a process of self-evaluation, whether it satisfies these prerequisites. The Scheme contains no provision, under any circumstance, for external inspection or assessment, either of a competent national authority or of a manufacturing facility. However, should a Member State or regional organization so wish, it could approach WHO, or a well-recognized drug regulatory authority, to occasionally delegate consultants to act as advisers in the course of national inspections and inspector training activities.
- ### 3. Requesting a certificate
- 3.1 Three documents can be requested within the scope of the Scheme:
- a certificate of a pharmaceutical product (product certificate);
  - a statement of licensing status of pharmaceutical product(s); and
  - a batch certificate of a pharmaceutical product.
- 3.2 Proposed formats for these documents are provided in Appendices 1, 2 and 3 of these guidelines. All participating Member States and regional authorities are henceforth urged to adopt these formats to facilitate interpretation of certified information. Requests for the provision of certificates offering

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more limited attestations, for instance, that the manufacturer complies with GMP or that the product is authorized for “free sale” within the country of export are discouraged. Similarly, requests should not be made for certification of information going beyond the scope of this Scheme. When manufacture takes place in a country other than that from which the product certificate is issued, an attestation relevant to compliance of the manufacture with GMP may still be provided (as an attachment to the product certificate) on the basis of inspections undertaken for registration purposes.

The Explanatory Notes attached to the three documents referred to above are very important. Whilst they are not part of the document to be certified, they should always be attached to the certificate.

- 3.3 A list of addresses of competent national regulatory authorities participating in the Scheme that are responsible for the registration of pharmaceutical and/or veterinary products, together with details of any reservations they have declared regarding their participation in the Scheme will be available at the WHO official website as indicated in section 2.6.
- 3.4 Each competent authority in certifying members should issue guidelines to all agents responsible for importing pharmaceutical products for human and/or veterinary use that operate under its jurisdiction, including those responsible for public sector purchases, to explain the contribution of certification to the drug regulatory process and the circumstances in which each of the three types of documents will be required.

#### Certificate of a pharmaceutical product

- 3.5 The Certificate of a pharmaceutical product (Appendix 1) issued by the competent authority in the exporting country or regional authority (“the certifying authority”), is intended for use by the competent authority in an importing country and regional organization in two situations:
- when the product in question is under consideration for a marketing authorization that will authorize its importation and sale;
  - when administrative action is required to renew, extend, vary or review such a marketing authorization.
- 3.6 The Certificate of a pharmaceutical product should not be required by the Member States or regulatory authorities where they undertake full quality, safety and efficacy review by themselves.
- 3.7 All requests for certificates should be channeled through the agent in the importing country (see

section 3.4) and the marketing authorization holder or other commercially-interested party in the exporting country (“the applicant”). The applicant should submit the following information for each product to the authority issuing the certificate:

- name and dosage form of product
- name and amount of active ingredient(s) per unit dose (International Nonproprietary Name(s) where such exist(s)),
- name and address of marketing authorization holder and/or manufacturing facility,
- formula (complete composition including all excipients; also particularly when no marketing authorization exists or when the formulation differs from that of the authorized product),
- product information for health professionals and for the public (patient information leaflets) as approved by the certifying authority,

For product information to be attached to the certificate see section 4.7

- 3.8 The certificate is a confidential document. As such, it can be issued by the certifying authority only with the permission of the applicant and, if different, of the marketing authorization holder.
- 3.9 The certificate is intended to be incorporated into a marketing authorization application in the competent authority in the importing country and regional authority (“the requesting authority”). Once prepared, it is transmitted to the requesting authority through the applicant and, when applicable, the agent in the importing country.
- 3.10 When any doubt arises about the status or validity of a certificate, the requesting authority should request a copy directly from the certifying authority, as provided for under section 4.9 of these guidelines.
- 3.11 In the absence of any specific agreement, each certificate will be prepared exclusively in the working language(s) of the certifying authority. The applicant will be responsible for providing any notarized translation that may be required by the requesting authority.
- 3.12 Since the preparation of certificates imposes a significant administrative load on certifying authorities, the service may need to be financed by charges levied upon applicants.
- 3.13 Supplementary attestations are obtainable only at the discretion of the certifying authority and with the permission of the applicant. The certifying authority is under no obligation to supply additional information. Requests for supplementary

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information should consequently be referred to the applicant, and only in exceptional circumstances to the certifying authority.

**Statement of marketing authorization**

3.14 Model statement of marketing authorization (Appendix 2). This attests only that a marketing authorization has been issued for a specified product, or products, for use in the exporting country. It is intended for use by importing agents when considering bids made in response to an international tender, in which case it should be requested by the agent as a condition of bidding. It is intended only to facilitate the screening and preparation of information. The importation of any product that is provisionally selected through this procedure should be determined on the basis of a CPP.

**Batch certificate**

3.15 A batch certificate of a pharmaceutical product (Appendix 3) refers to an individual batch of a pharmaceutical product and is a vital instrument in drug procurement. The provision of a batch certificate is usually a mandatory element in tender and procurement documents.

3.16 A batch certificate is normally issued by the manufacturer and only exceptionally, as in the case of vaccines, sera and some other biological products, by the competent authority in the exporting country or regional authority. The batch certificate is intended to accompany and provide an attestation concerning the quality and expiry date of a specific batch or consignment of a product that has already obtained market authorization in the importing country. The batch certificate should include the specifications of the final product at the time of batch release and the results of a full analysis undertaken on the batch in question. In most circumstances these certificates are issued by the manufacturer to the importing agent (*i.e.* the marketing authorization holder in the importing country), but they must be made available at the request of – or in the course of any inspection made on behalf of – the competent authority.

**4. Issuing a certificate**

4.1 The certifying authority is responsible for assuring the authenticity of the certified data. Certificates should not bear the WHO emblem, but a statement should always be included to confirm whether or not the document is issued in the format recommended by WHO.

4.2 When the applicant is the manufacturer of the finished dosage form, the certifying authority

should satisfy itself, before attesting compliance with GMP, that the applicant:

- applies identical GMP standards to the production of all batches of pharmaceutical products manufactured within the facility, including those destined exclusively for export;
- consents, in the event of identification of a quality defect consonant with the criteria set out in section 5.1, to relevant inspection reports being released, in confidence, to the requesting authority, should the latter so require.

4.3 When the applicant is not the manufacturer of the finished dosage form, the certifying authority should similarly satisfy itself – in so far as it has authority to inspect the records and relevant activities of the applicant – that it has the applicant's consent to release relevant reports on the same basis as described in section 4.2 (b) above.

4.4 GMP as recommended by WHO assigns to the manufacturer of the finished dosage form responsibility for assuring the quality of APIs. National or regional regulations may require that suppliers of APIs be identified in the marketing authorization, but the competent authority may have no power to inspect them.

4.5 Notwithstanding this situation, a certifying authority may agree, on a discretionary and voluntary basis, and at the request of a manufacturer, to undertake an inspection of a manufacturer of APIs to satisfy specific requirements of a requesting authority. Alternatively, pending the development of specific guidelines for APIs, the certifying authority may be able to attest that the manufacturer is an established supplier of the substance in question to manufacturers of finished dosage forms authorized for marketing under its jurisdiction.

4.6 Whenever a product is purchased through a broker or another intermediary, or when more than one set of premises has been involved in the manufacture and packaging of a product, the certifying authority should consider whether it has received sufficient information to satisfy itself that those aspects of the manufacture of the product for which the applicant is not directly responsible have been undertaken in compliance with GMP as recommended by WHO.

4.7 The certifying authority should officially stamp and date all copies of product information submitted to it in support of an application for a certificate and intended to be appended to the certificate.

Every effort should be made to ensure that certificates and all annexed documentation are



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consonant with the version of the marketing authorization operative on the date of issue. Nevertheless, requesting authorities should not request unnecessary legalization procedure that may cause undue delay of certificates.

When available, the certifying authority will add a summary basis of approval or any other material the authority deems relevant. Translation by an applicant of these materials into a widely used language, preferably English, shall be deemed to satisfy the provision of 3.11.

4.8 Any additional attachment to a certificate submitted by the applicant, such as price lists of products for which bids are offered, should be clearly identified as not comprising part of the attestation made by the certifying authority.

4.9 To avert potential abuse of the Scheme, to frustrate attempts at falsification, to render routine authentication of certificates by an independent authority superfluous and to enable the certifying authority to maintain comprehensive records of countries to which specific products have been exported, each certificate should identify the importing country and be stamped on each page with the official seal of the certifying authority.

If requested, an identical copy, clearly marked as duplicate, should be forwarded by the certifying authority on demand directly to the requesting authority.

4.10 The certifying authority should establish standard period of time for issue of certificates. It should endeavor to make each issue of certificate completed within this period as far as the applicant submits sufficient documents.

## 5. Notifying and investigating a quality defect

5.1 Each certifying authority undertakes to institute enquiries into any quality defect reported in a product exported in accordance with the provisions of the Scheme, on the understanding that:

- the complaint is transmitted, together with the relevant facts, through the requesting authority;
- the complaint is considered to be of a serious nature by the latter authority; and
- the defect, if it appeared after delivery of the product into the importing country, is not attributable to local conditions.

5.2 In the case of obvious doubt, a participating national authority may request WHO to assist in identifying

an independent quality control laboratory to carry out tests for the purposes of quality control.

5.3 Each certifying authority undertakes to inform WHO and, as far as is possible, all competent national authorities, of any serious hazard newly associated with a product exported under the provisions of the Scheme or of any criminal abuse of the Scheme directed, in particular, to the export of falsely labelled, substandard or falsified pharmaceutical products. On receipt of such notification, WHO will transmit the message immediately to the competent authority in each Member State and regional organization.

5.4 WHO stands prepared to offer advice should difficulty arise in implementing any aspect of the Scheme or in resolving a complaint, but it cannot be a party to any resulting litigation or arbitration.

## References

1. Quality control of drugs. In: *Twenty-second World Health Assembly, Boston, Massachusetts, 8-25 July 1969. Part 1: Resolutions and decisions, annexes*. Geneva, World Health Organization, 1969: 99-105 (Official Records of the World Health Organization, No. 176).
2. Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: *Twenty-eighth World Health Assembly, Geneva, 13-30 May 1975. Part 1: Resolutions and decisions, annexes*. Geneva, World Health Organization, 1975: 94-95 (Official Records of the World Health Organization, No. 226).
3. WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: *Forty-first World Health Assembly, Geneva, 2-13 May 1988. Resolutions and decisions, annexes*. Geneva, World Health Organization, 1988: 53-55 (WHA41/1988/REC/1).
4. Proposed guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: *Forty-fifth World Health Assembly, Geneva, 4-14 May 1992. Resolutions and decisions, annexes*. Geneva, World Health Organization, 1992: 155-165 (Document WHA41/1992/REC/1).
5. Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: *Forty-fifth World Health Assembly, Geneva, 5-14 May 1997. Resolutions and decisions, annexes*. Geneva, World Health Organization, 1997: 2-3 (WHA50/1997/REC/1).

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**Appendix 1**

**Model Certificate of a Pharmaceutical Product**  
**Certificate of a pharmaceutical product<sup>1</sup>**

This certificate conforms to the format recommended by the World Health Organization (WHO)  
 (general instructions and explanatory notes attached)

No. of Certificate: \_\_\_\_\_

Certifying member (certifying country): \_\_\_\_\_

Requesting member (requesting country): \_\_\_\_\_

1. Name and dosage form of the product: \_\_\_\_\_

1.1. Active ingredient(s)<sup>2</sup> and amount(s) per unit dose<sup>3</sup>: \_\_\_\_\_

\_\_\_\_\_

For complete composition including excipients, see attached.<sup>4</sup>

1.2. Is this product authorized to be placed on the market for use in the exporting country?<sup>5</sup>  
 yes/no \_\_\_\_\_ (key in as appropriate)

1.3. Is this product actually on the market in the exporting country?  
 yes/no/unknown \_\_\_\_\_ (key in as appropriate)  
 If the answer to 1.2. is yes, continue with section 2A and omit section 2B.  
 If the answer to 1.2 is no, omit section 2A and continue with section 2B<sup>6</sup>:

2.A.1. Number of marketing authorization<sup>7</sup> and date of issue: \_\_\_\_\_

2.A.2. Marketing authorization holder (name and address): \_\_\_\_\_

2.A.3. Status of marketing authorization holder<sup>8</sup>:  
 a/b/c/d \_\_\_\_\_ (key in appropriate category as defined in note 8)

2.A.3.1. For categories b, c and d, the name and address of the manufacturer producing the dosage form is<sup>9</sup>: \_\_\_\_\_

2.A.3.2. For categories d, the name and address of the manufacturer certifying the finished pharmaceutical product batch is:<sup>9</sup> \_\_\_\_\_

2.A.4. Is a summary basis for approval appended? <sup>10</sup> yes/no \_\_\_\_\_ (key in as appropriate)

2.A.5. Is the attached, officially approved product information complete and consonant with the market authorization? <sup>11</sup> yes/no/not provided \_\_\_\_\_ (key in as appropriate)

2.A.6. Applicant for certificate, if different from licence holder (name and address)<sup>12</sup>: \_\_\_\_\_

2.B.1. Applicant for certificate (name and address): \_\_\_\_\_

2.B.2. Status of applicant: a/b/c/d \_\_\_\_\_ (key in appropriate category as defined in footnote 8)



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- 2.B.2.1. For categories b, c and d the name and address of the manufacturer producing the dosage form is:<sup>9</sup>  
\_\_\_\_\_
- 2.B.2.2. For categories d, the name and address of the manufacturer certifying the finished pharmaceutical product batch is<sup>9</sup>  
\_\_\_\_\_
- 2.B.3. Why is marketing authorization lacking?  
not required/not requested/under consideration/refused \_\_\_\_\_ (*key in as appropriate*)
- 2.B.4. Remarks<sup>13</sup>: \_\_\_\_\_  
\_\_\_\_\_
3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? yes/no/not applicable<sup>14</sup> \_\_\_\_\_ (*key in as appropriate*)  
If not or not applicable, proceed to question 4.
- 3.1. Periodicity of routine inspections (years): \_\_\_\_\_
- 3.2. Has the manufacture of this type of dosage form been inspected?  
yes/no \_\_\_\_\_ (*key in as appropriate*)
- 3.3. Do the facilities and operations conform to GMP as recommended by WHO? <sup>15</sup>  
yes/no/not applicable<sup>14</sup> \_\_\_\_\_ (*key in as appropriate*)
4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product? <sup>16</sup> yes/no \_\_\_\_\_ (*key in as appropriate*)  
If no, explain: \_\_\_\_\_  
\_\_\_\_\_

Address of certifying authority: \_\_\_\_\_  
\_\_\_\_\_

Telephone number: \_\_\_\_\_ Fax number: \_\_\_\_\_

Email address: \_\_\_\_\_

Name of authorized person: \_\_\_\_\_

Signature: \_\_\_\_\_

Stamp and date: \_\_\_\_\_

**General instructions**

Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the Scheme.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

**Explanatory notes**

- <sup>1</sup> This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.
- <sup>2</sup> Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.
- <sup>3</sup> The formula (complete composition) of the dosage form should be given on the certificate or be appended.
- <sup>4</sup> Details of quantitative composition are preferred but their provision is subject to the agreement of the marketing authorization holder.
- <sup>5</sup> When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the marketing authorization.

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- <sup>6</sup> Sections 2A and 2B are mutually exclusive.
- <sup>7</sup> Indicate, when applicable, if the licence is provisional, or the product has not yet been approved.
- <sup>8</sup> Specify whether the person responsible for placing the product on the market:
- (a) manufactures the dosage form;
  - (b) packages and/or labels a dosage form manufactured by an independent company;
  - (c) certifies the finished pharmaceutical product batch; or
  - (d) is involved in none of the above.
- <sup>9</sup> This information can only be provided with the consent of the marketing authorization holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information. It should be noted that information concerning the site of production is part of the marketing authorization. If the production site is changed, the marketing authorization has to be updated or it is no longer valid.
- <sup>10</sup> This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.
- <sup>11</sup> This refers to product information approved by the competent national drug regulatory authority, such as summary product characteristics
- <sup>12</sup> In this circumstance, permission for issuing the certificate is required from the marketing authorization holder. This permission has to be provided to the authority by the applicant.
- <sup>13</sup> Please indicate the reason that the applicant has provided for not requesting registration.
- (a) the product has been developed exclusively for the treatment of conditions – particularly tropical diseases – not endemic in the country of export;
  - (b) the product has been reformulated with a view to improving its stability under tropical conditions; the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;
  - (c) the product has been reformulated to meet a different maximum dosage limit for an active ingredient; any other reason, please specify.
- <sup>14</sup> Not applicable means the manufacture is taking place in a country other than that issuing the product certificate and inspection is conducted under the aegis of the country of manufacture.
- <sup>15</sup> The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series, No. 823, 1992, Annex 1. Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).
- <sup>16</sup> This section is to be completed when the marketing authorization holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.
-

## Proposal for revision of the WHO Certification Scheme

**Appendix 2****Model Statement of Marketing Authorization Status of Pharmaceutical Product(s)**

No. of Statement: \_\_\_\_\_

Certifying member (certifying country): \_\_\_\_\_

Requesting member (requesting country): \_\_\_\_\_

**Statement of marketing authorization of pharmaceutical product(s) <sup>1</sup>**

This statement indicates **only** whether or not the following products are licensed to be put on the market in the exporting country.

Applicant (name/address): \_\_\_\_\_

Name of product	Dosage form	Active ingredient(s) <sup>2</sup> and amount(s) per unit dose:	Marketing authorization no. and date of issue <sup>3</sup>

The certifying authority undertakes to provide, at the request of the applicant (or, if different, the marketing authorization holder), a separate and complete certificate of a pharmaceutical product (CPP) in the format recommended by the World Health Organization (WHO), for each of the products listed above.

Address of certifying authority: \_\_\_\_\_

Telephone number: \_\_\_\_\_ Fax number: \_\_\_\_\_

Email address: \_\_\_\_\_

Name of authorized person: \_\_\_\_\_

Signature: \_\_\_\_\_

Stamp and date: \_\_\_\_\_

This statement conforms to the format recommended by WHO.

**General instructions**

Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the Scheme.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

**Explanatory notes**

<sup>1</sup> This statement is intended for use by importing agents who are required to screen bids made in response to an international tender and should be requested by the agent as a condition of bidding. The statement indicates that the listed products are authorized to be placed on the market for use in the exporting country. A CPP in the format recommended by WHO will be provided, at the request of the applicant and, if different, the marketing authorization holder, for each of the listed products.

<sup>2</sup> Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.

<sup>3</sup> If no marketing authorization has been granted, enter "not required", "not requested", "under consideration" or "refused" as appropriate.

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**Proposal for revision of the WHO Certification Scheme****Appendix 3****Model Batch Certificate of a Pharmaceutical Products  
Manufacturers/Official<sup>1</sup> Batch Certificate of a Pharmaceutical Product**

This certificate conforms to the format recommended by the World Health Organization (WHO) (*general instructions and explanatory notes attached*).

1. No. of Certificate: \_\_\_\_\_
2. Importing (requesting) authority: \_\_\_\_\_
3. Name of product: \_\_\_\_\_
- 3.1. Dosage form: \_\_\_\_\_
- 3.2. Active ingredient(s)<sup>2</sup> and amount(s) per unit dose: \_\_\_\_\_  
\_\_\_\_\_
- 3.2.1 Is the composition of the product identical to that registered in the country of export?  
(yes/no/not applicable)<sup>3</sup>  
If no: please attach formula (including excipients) of both products.
4. Marketing authorization holder<sup>4</sup> (name and address): \_\_\_\_\_  
\_\_\_\_\_
- 4.1 Marketing authorization number<sup>4</sup>: \_\_\_\_\_
- 4.2 Date of issue<sup>4</sup>: \_\_\_\_\_
- 4.3 Marketing authorization issued by<sup>4</sup>: \_\_\_\_\_
- 4.4 Product certificate number<sup>4,5</sup>: \_\_\_\_\_
- 5.1 Batch number: \_\_\_\_\_
- 5.2 Date of manufacture: \_\_\_\_\_
- 5.3 Shelf life (years): \_\_\_\_\_
- 5.4 Contents of container: \_\_\_\_\_
- 5.5 Nature of primary container: \_\_\_\_\_
- 5.6 Nature of secondary container/wrapping: \_\_\_\_\_
- 5.7 Specific storage conditions: \_\_\_\_\_
- 5.8 Temperature range: \_\_\_\_\_
6. Remarks<sup>6</sup>: \_\_\_\_\_  
\_\_\_\_\_
7. Quality analysis:
  - 7.1 What specifications apply to this dosage form. Either specify the pharmacopoeia or append company specifications.<sup>7</sup>  
\_\_\_\_\_
  - 7.1.1 In the case of a product registered in the exporting country, have these company specifications<sup>7</sup> been accepted by the competent authority? (yes/no)

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 Proposal for revision of the WHO Certification Scheme

- 7.2 Does the batch comply with all parts of the above specifications?  
yes/no \_\_\_\_\_ (*key in as appropriate*)
- 7.3 Append certificate of analysis<sup>8</sup>

It is hereby certified that the above declarations are correct and that the results of the analyses and assays on which they are based will be provided on request to the competent authorities in both the importing and exporting countries.

Name and address of authorized person: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Telephone number: \_\_\_\_\_ Fax number: \_\_\_\_\_

Email address: \_\_\_\_\_

Name of authorized person: \_\_\_\_\_

Signature: \_\_\_\_\_

Stamp and date: \_\_\_\_\_

### General instructions

Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the Scheme.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

### Explanatory notes

Certification of individual batches of a pharmaceutical product is only undertaken exceptionally by the competent authority of the exporting country. Even then, it is rarely applied other than to vaccines, sera and biologicals. For other products, the responsibility for any requirement to provide batch certificates rests with the marketing authorization holder in the exporting country. The responsibility to forward certificates to the competent authority in the importing country is most conveniently assigned to the importing agent.

Any inquiries or complaints regarding a batch certificate should always be addressed to the competent authority in the exporting country. A copy should be sent to the marketing authorization holder.

- <sup>1</sup> Strike out whichever does not apply.
- <sup>2</sup> Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.
- <sup>3</sup> "Not applicable" means that the product is not registered in the country of export.
- <sup>4</sup> All items under 4 refer to the marketing authorization or the certificate of a pharmaceutical product (CPP) issued in the exporting country.
- <sup>5</sup> This refers to the CPP as recommended by WHO.
- <sup>6</sup> Indicate any special storage conditions recommended for the product as supplied.
- <sup>7</sup> For each of the parameters to be measured, specifications give the values that have been accepted for batch release at the time of product registration.
- <sup>8</sup> Identify and explain any discrepancies from specifications. Government batch release certificates issued by certain governmental authorities for specific biological products provide additional confirmation that a given batch has been released, without necessarily giving the results of testing. The latter are contained in the manufacturer's certificate of analysis.

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**Proposal for revision of the WHO Certification Scheme****Appendix 4****Glossary and index**

In order to facilitate understanding, this glossary explains terms in the guidelines and/or refers to relevant sections. It is considered as supplementary information and not as being a formal part of the Scheme.

**abuse of Scheme.** See section 4.9 and 5.2 of the guidelines.

**active pharmaceutical ingredients.** Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

**addresses of competent authorities.** See item 2.6 and 3.3 of the guidelines.

**applicant.** The party applying for a product certificate. This is normally the marketing authorization holder. In all instances, having regard to commercial confidentiality of certain data, the competent authority in the exporting country must obtain permission to release these data from the marketing authorization holder, or, in the absence of a marketing authorization, from the manufacturer.

**authentication of certificates.** See section 4.9 of the guidelines.

**batch (or lot).** A defined quantity of a starting material, packaging material, or product processed in a single process or series of processes so that it can be expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quality or as the amount produced in a final time interval.

**batch certificate.** A document containing information, as set out in Annex 3 of the guidelines for use, will normally be issued for each batch by the manufacturer. Furthermore, exceptionally a batch certificate may be validated or issued by the competent authority of the exporting country, particularly for vaccines, sera and other biological products. The batch certificate travels with every major consignment (see also section 3.14 of the guidelines).

**batch number (or lot number).** A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

**bulk product.** Any product that has completed all processing stages up to, but not including, final packaging.

**certifying authority.** This is the competent authority that issues product certificates. It shall ensure that it possesses the capacities listed in section 2.2 and 2.3 of the guidelines.

**charges for product certificates.** See section 3.11 of the guidelines.

**competence and evaluation of national authority.** See sections 2.2, 2.3, 2.9 and 4.2 of the guidelines.

**competent authority.** This is the national or regional authority as identified in the formal letter of acceptance in which each Member State or regional authority informs WHO of its intention to participate in the Scheme. The competent authority can issue or receive certificates. The extent of participation should be indicated in the letter of acceptance. (see section 2.1 of the guidelines)

WHO makes available a continuously updated list of addresses of competent authorities and the specific conditions for participation (see section 2.6 of the guideline).

**dosage form.** The form of the completed pharmaceutical product, e.g. tablet, capsule, elixir, suppository.

**drug regulatory authority.** A national or regional authority responsible for the registration of and other regulatory activities connecting pharmaceutical products.

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**Proposal for revision of the WHO Certification Scheme**

**expiry date.** The date given on the individual container (usually on the label) of a product up to and including which the product is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf life to the date of manufacture.

**finished pharmaceutical product.** A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

**free sale certificate.** See section 3.2 of the guidelines.

**good manufacturing practices.** That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

**good manufacturing practices certificate.** See section 3.2 of the guidelines.

**importing agents,** guidelines for. See section 3.4 of the guidelines.

**International Nonproprietary Name (INN).** The shortened scientific name based on the active ingredient. WHO is responsible for assigning INNs to pharmaceutical substances.

**language of product certificates.** See section 3.10 of the guidelines.

**limits of certification by competent authority.** See section 3.12 and 4.8 of the guidelines.

**\*manufacture.** All operations of purchase of materials and products, production, quality control, release, storage, distribution of pharmaceutical products, and related controls.

**\*manufacturer.** A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals. (for categories of manufacturer, see Appendix 1, Explanatory Note No. 7).

**marketing authorization.** A legal document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INNs or national generic names where they exist), the shelf life and storage conditions and packaging characteristics. It specifies the information on which authorization is based (e.g. "The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence."). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products – the register – and is often said to be "registered" or to "have registration". Market authorization may occasionally also be referred to as a "licence" or "product licence".

**marketing authorization holder.** An individual or a corporate entity being in the possession of a marketing authorization of a pharmaceutical product.

**pharmaceutical product.** Any material and product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in exporting state and/or the importing state.

**product.** See pharmaceutical product.

**product certificate.** A document containing the information as set out in Appendix 1 of the guidelines that is validated and issued for a specific product by the competent authority of the exporting country or regional authority and intended for use by the competent authority in the importing country or – in the absence of such an authority – by the drug procurement authority (see also section 3.5 of the guidelines).

**product information.** This is the approved product information referred to in section 4.7 of the guidelines and item 2.A.5 of the product certificate. It normally consists of information for health professionals and the public (patient information leaflets) as approved in the exporting country, and when available, a data sheet or a summary of product characteristics approved by the drug regulatory authority.

**production.** All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

### Proposal for revision of the WHO Certification Scheme

**registration.** Any statutory system of approval required at national or regional level as a precondition for introducing a pharmaceutical product onto the market.

**specifications.** A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

**statement of licensing status.** See section 3.13 of the guidelines and Annex 2

**summary basis of approval.** This refers to the document prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed (see section 4.7 of the guidelines and explanatory note 9 of the product certificate contained in Annex 1).

**Summary product characteristics (SPC).** Product information as approved by the drug regulatory authority. The SPC serves as the basis for production of information for health personnel as well as for consumer information on labels and leaflets of medicinal products and for control of advertising (see also product information).

**tenders and brokers.** See section 4.6 of the guidelines.

**transmission of product certificate.** See section 3.8 and 4.9 of the guidelines.

**validity of product certificate.** See section 3.9 of the guidelines.

**when to request a product certificate.** See item 3.5 of the guidelines.

**WHO responsibility.** See item 5.4 of the guidelines.

### References

1. WHO good distribution practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Forty-fourth report. Geneva, World Health Organization, 2010, Annex 5 (WHO Technical Report Series, No. 957).
2. WHO guidelines on quality risk management. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Forty-seventh report. Geneva, World Health Organization, 2013, Annex 2 (WHO Technical Report Series, No. 981).
3. WHO good manufacturing practices for pharmaceutical products: main principles. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Forty-eighth report. Geneva, World Health Organization, 2014, Annex 2 (WHO Technical Report Series, No. 986).
4. Model quality assurance system for procurement agencies. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Forty-eighth report. Geneva, World Health Organization, 2014, Annex 3 (WHO Technical Report Series, No. 986).

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## Other recent WHO consultation documents

**The following new or revised guidelines have recently been posted for public comment on the WHO website** ([www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects)).

### **Revision of WHO GMP for sterile pharmaceutical products – a joint EU, PIC/S, WHO project**

Working document QAS/17.745, December 2017

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

### **Good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms: Part 2. Interpretation of part 1 – GMP for HVAC systems.**

Working document QAS/18.759, February 2018

This document represents Part 2 of the heating, ventilation and air-conditioning (HVAC) systems guidelines. It contains non-binding examples, drawings, technical representations and interpretation in support of Part 1 of the HVAC systems guidelines.

### **Guidelines on import procedures for pharmaceutical products (revision)**

Working document QAS/18.773, May 2018

This is a revision of the WHO guidelines published in 1996. They are intended to promote efficiency in applying relevant regulations, to simplify the checking and handling of consignments of pharmaceutical products in international transit and to provide a basis for collaboration between all parties involved in importation of medicines.

### **Validation of computerized systems (Appendix 5 to Guidelines on Validation)**

Working document QAS/16.667/Rev.1, May 2018

This is a revision of the 2006 WHO guidance on validation of computerized systems. It applies to systems used in good manufacturing practices (GMP) but may be extended to systems used in all good practice (GXP) activities, as appropriate. ○

# ATC/DDD classification

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

## ATC/DDD classification (temporary)

The following ATC codes and DDDs were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in March 2018. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology before 1 September 2018. If no objections are received before this date, the new ATC codes and DDDs will be considered final and included in the **January 2019 version of the ATC/DDD Index**.

### New ATC 5<sup>th</sup> level codes

ATC level name/INN	ATC code
abemaciclib	L01XE50
angiotensin II	C01CX09
apalutamide	L02BB05
avatrombopag	B02BX08
candesartan, amlodipine and hydrochlorothiazide	C09DX06
cannabidiol	N03AX24
cefpodoxime and beta-lactamase inhibitor	J01DD64
copanlisib	L01XX61
doravirine	J05AG06
edaravone	N07XX14
fexinidazole	P01CA03
fostamatinib	B02BX09
gemigliptin and rosuvastatin	A10BH52
hydrogen peroxide	D11AX25
ibalizumab	J05AX23
lamivudine, tenofovir disoproxil and doravirine	J05AR24
leuprorelin and bicalutamide	L02AE51
metformin, saxagliptin and dapagliflozin	A10BD25

*Continued*

Temporary

*New ATC 5<sup>th</sup> level codes (continued)*

ATC level name/INN	ATC code
omidenepeg	S01EX06
prasterone	G03XX01
talazoparib	L01XX60
telotristat	A16AX15
trifarotene	D10AD06

*New ATC level codes (other than 5<sup>th</sup> levels)*

ATC level name/INN	ATC code
Other sex hormones and modulators of the genital system	G03XX

*Change of ATC code*

ATC level name/INN	Previous ATC code	New ATC code
dimethyl fumarate	N07XX09	L04AX07

*Changes of ATC level names*

Previous	New	ATC code
Angiotensin II antagonists, plain	Angiotensin II receptor blockers (ARBs), plain	C09C
Angiotensin II antagonists, plain	Angiotensin II receptor blockers (ARBs), plain	C09CA
Angiotensin II antagonists, combinations	Angiotensin II receptor blockers (ARBs), combinations	C09D
Angiotensin II antagonists and diuretics	Angiotensin II receptor blockers (ARBs) and diuretics	C09DA
Angiotensin II antagonists and calcium channel blockers	Angiotensin II receptor blockers (ARBs) and calcium channel blockers	C09DB
Angiotensin II antagonists, other combinations	Angiotensin II receptor blockers (ARBs), other combinations	C09DX
fluoromethylcholine (18F)	fluorocholine (18F)	V09IX07
combinations	potassium (different salts in combination)	A12BA30

*New DDDs*

ATC level name/INN	DDD	unit	Adm.R*	ATC code
artemether	0.28	g	R	P01BE02
artesunate	0.28	g	R	P01BE03
benralizumab	0.54	mg	P	R03DX10
chenodeoxycholic acid	1	g	O	A05AA01
cladribine	0.34	mg	O	L04AA40
dupilumab	21.4	mg	P	D11AH05

Continued

## Temporary

*New DDDs (continued)*

ATC level name/INN	DDD	unit	Adm.R*	ATC code
emicizumab	15	mg	P	B02BX06
ertugliflozin	10	mg	O	A10BK04
guselkumab	1.79	mg	P	L04AC16
letermovir	0.48	g	O,P	J05AX18
ocrelizumab	3.29	mg	P	L04AA36
patiromer calcium	8.4	g	O	V03AE09
rolapitant	0.18	g	O	A04AD14
telotristat	0.75	g	O	A16AX15

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

*Changes of DDDs*

ATC level name/INN	Previous DDD			New DDD			ATC code
	DDD	Unit	Adm.R.*	DDD	Unit	Adm.R.*	
aprepitant <sup>1</sup>	95	mg	P	150	mg	P	A04AD12
aprepitant	95	mg	O	165	mg	O	A04AD12
temocillin	2	g	P	4	g	P	J01CA17
vasopressin (argipressin)	4	U	P	40	U	P	H01BA01

\* Administration Route: P=parenteral.

<sup>1</sup> expressed as fosaprepitant

WHO Collaborating Centre for Drug Statistics Methodology  
Oslo, May 2018

## ATC/DDD classification (final)

The following ATC codes and DDDs were agreed at the meeting of the WHO International Working Group for Drug Statistics Methodology in October 2017. These are considered final and included in the **January 2019 version of the ATC/DDD Index**.

### *New ATC 5<sup>th</sup> level codes*

<b>ATC level name/INN</b>	<b>ATC code</b>
ambrisentan and tadalafil	C02KX52
atazanavir and ritonavir	J05AR23
atezolizumab	L01XC32
avelumab	L01XC31
caplacizumab	B01AX07
cefteram	J01DD18
cladribine <sup>†</sup>	L04AA40
clenbuterol and ambroxol	R03CC63
crisaborole	D11AH06
crofelemer	A07XA06
cytarabine and daunorubicin	L01XY01
dacomitinib	L01XE47
dapivirine	G01AX17
delafloxacin	J01MA23
doxepin	D04AX01
emapalumab	L04AA39
enasidenib	L01XX59
encorafenib	L01XE46
enisamium iodide	J05AX17
epacadostat	L01XX58
eravacycline	J01AA13
ertugliflozin	A10BK04
fexapotide	G04CX04
floxuridine	L01BC09
galcanezumab	N02CX08
glecaprevir and pibrentasvir	J05AP57
ibandronic acid and colecalciferol	M05BB09
icotinib	L01XE48
imidazolyl ethanamide pentandioic acid	J05AX21
indocyanine green	V04CX01
ipragliflozin	A10BK05
isoniazid, sulfamethoxazole, trimethoprim and pyridoxine	J04AM08
kagocel	J05AX22
lanadelumab	B06AC05

*Continued*

## Final

*New ATC 5<sup>th</sup> level codes (continued)*

ATC level name/INN	ATC code
letermovir	J05AX18
lorlatinib	L01XE44
lusutrombopag	B02BX07
medroxyprogesterone and estradiol	G03AA17
meropenem and vaborbactam	J01DH52
metformin and ertugliflozin	A10BD23
naldemedine	A06AH05
neratinib	L01XE45
norgestimate and ethinylestradiol	G03AB09
ozanimod	L04AA38
patisiran	N07XX12
peramivir	J05AH03
riboflavin	S01XA26
rifampicin, ethambutol and isoniazid	J04AM07
roxadustat	B03XA05
sitagliptin and ertugliflozin	A10BD24
tebipenem pivoxil	J01DH06
tildrakizumab	L04AC17
tilorone	J05AX19
tosufloxacin	J01MA22
uramustine	L01AD08
vaginal ring with progestogen	G02BB02
valbenazine	N07XX13
valsartan and nebivolol	C09DX05

- 1** Oral formulations indicated for multiple sclerosis.  
Parenteral formulations are classified in L01BB04.

*Change of ATC level name*

Previous	New	ATC code
dinutuximab	dinutuximab beta	L01XC16

*New DDDs*

ATC level name/INN	DDD	Unit	Adm.R*	ATC code
atazanavir and ritonavir	0.3	g <sup>1</sup>	O	J05AR23
baricitinib	4	mg	O	L04AA37
cariprazine	3	mg	O	N05AX15
cefroxadine	2.1	g	O	J01DB11
cefteram	0.4	g	O	J01DD18
ceftriaxone and beta-lactamase inhibitor	2	g <sup>2</sup>	P	J01DD63
colistin	9	MU	O	A07AA10

*Continued*

*New DDDs (continued)*

ATC level name/INN	DDD	Unit	Adm.R*	ATC code
delafloxacin	0.9	g	O	J01MA23
delafloxacin	0.6	g	P	J01MA23
delamanid	0.2	g	O	J04AK06
desfesoterodine	3.5	mg	O	G04BD13
droxidopa	1	g	O	C01CA27
eluxadoline	0.2	g	O	A07DA06
enisamium iodide	1.5	g	O	J05AX17
estradiol	1.53	mg	TD spray	G03CA03
faropenem	0.75	g	O	J01DI03
follitropin delta	12	mcg	P	G03GA10
garenoxacin	0.4	g	O	J01MA19
gemifloxacin	0.32	g	O	J01MA15
imidazolyl ethanamide pentandioic acid	90	mg	O	J05AX21
insulin glargine and lixisenatide	40	U <sup>3</sup>	P	A10AE54
kagocel	60	mg	O	J05AX22
kanamycin	3	g	O	A07AA08
lomefloxacin	0.4	g	O	J01MA07
mepyramine theophyllinacetate	0.6	g	O	R03DA12
midecamycin	1.2	g	O	J01FA03
misoprostol	0.2	mg	O	G02AD06
naldemedine	0.2	mg	O	A06AH05
nusinersen	0.1	mg	P	M09AX07
pyrimethamine, combinations	75	mg <sup>4</sup>	P	P01BD51
reslizumab	7.1	mg	P	R03DX08
rimantadine	0.2	g	O	J05AC02
sarilumab	14.3	mg	P	L04AC14
secnidazole	2	g	O	P01AB07
tebipenem pivoxil	0.56	g	O	J01DH06
thyroid gland preparations	0.1	g	O	H03AA05
tilorone	0.125	g	O	J05AX19
tosufloxacin	0.45	g	O	J01MA22

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

**1** refers to atazanavir.

**2** refers to ceftriaxone.

**3** refers to insulin glargine.

**4** refers to pyrimethamine.

Final

*Changes of DDDs*

ATC level name/INN	Previous DDD			New DDD			ATC code
	DDD	Unit	Adm.R.*	DDD	Unit	Adm.R.*	
amoxicillin	1	g	O	1.5	g	O	J01CA04
amoxicillin	1	g	P	3	g	P	J01CA04
amoxicillin and beta-lactamase inhibitor <sup>1</sup>	1	g	O	1.5	g	O	J01CR02
ampicillin	2	g	P	6	g	P	J01CA01
cefepime	2	g	P	4	g	P	J01DE01
ciprofloxacin	0.5	g	P	0.8	g	P	J01MA02
colistin	3	MU	P	9	MU	P	J01XB01
meropenem	2	g	P	3	g	P	J01DH02

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

<sup>1</sup> New ATC level name valid from 2018.

WHO Collaborating Centre for Drug Statistics Methodology  
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