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Review | Обзорная статья

H. Schmidt[1] ✉,
J. Sawyer[1],
K. Zribi[2],
R. van der Werf[3]

The International Pharmacopoeia: Focus, Processes, Response to COVID-19 and Collaboration with other Pharmacopoeias

[1] *World Health Organisation, 20, avenue Appia, 1211 Geneva 27, Switzerland*

[2] *Faculty of Pharmacy, University of Monastir, 1, Ibn Sina Street, 5000 Monastir, Tunisia*

[3] *European Directorate for the Quality of Medicines & Healthcare, 7, allée Kastner, CS 30026, F-67081 Strasbourg, France*

✉ ***Herbert Schmidt***; *schmidth@who.int*

ABSTRACT

The World Health Organisation develops and promotes international standards for pharmaceutical products, in support of efforts to increase access to quality-assured medicines for all, and to safeguard patients from substandard and falsified medicines. The International Pharmacopoeia is a key output of this work. Its focus, processes to establish texts for inclusion or revision, response to COVID-19 and the collaboration with other Pharmacopoeias shall be discussed in this review. Pharmacopoeias provide public standards (written norms as well as physical reference standards), which ensure the quality of medicines by defining the attributes that are essential to their safety and efficacy. They consist of analytical methods to test for the identity, purity and content of pharmaceutical products, together with acceptance criteria to evaluate test results, and information about storage, labelling and production. Pharmacopoeias greatly facilitate the development of multi-source medicines (generics) by defining minimum quality standards that a group of medicines must meet in order to be considered of commensurate safety, quality and effectiveness as the originator product(s). The added value of The International Pharmacopoeia lies in its focus on monographs of particular relevance to low- and middle-income countries which may not have sufficient resources to develop national pharmacopoeias. In a globalised world, where medicines and health products are frequently sourced from several countries with differing regulatory standards and requirements, and when the response to Public Health Emergencies of International Concern, like the COVID-19 pandemic, necessitates swift and equitable access to urgently needed quality-assured therapeutics, such a resource is indispensable.

Key words: World Health Organisation; The International Pharmacopoeia; International Chemical Reference Substances; essential medicines; prequalification of medicines

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Г. Шмидт[1] ✉,
Ж. Сойер[1],
К. Зриби[2],
Р. ван дер Верф[3]

Международная фармакопея: основные направления деятельности, организация работы, борьба с COVID-19 и сотрудничество с другими фармакопеями

[1] *Всемирная организация здравоохранения, авеню Аппиа, д. 20, г. Женева, 27 (1211), Швейцария*

[2] *Фармацевтический факультет Университета г. Монастир, ул. Авиценны, д. 1, г. Монастир, 5000, Тунис*

[3] *Европейский директорат по качеству лекарственных средств и здравоохранению, аллея Кастнер, д. 7, г. Страсбург, CS 30026, F-67081, Франция*

✉ ***Герберт Шмидт***; *schmidth@who.int*

РЕЗЮМЕ

Всемирная организация здравоохранения (ВОЗ) занимается разработкой и распространением международных стандартов для лекарственных средств, чтобы обеспечить всеобщий доступ к гарантированно качественным препаратам и оградить пациентов от недоброкачественных и фальсифицированных лекарственных средств. Международная фармакопея — один из важнейших результатов работы ВОЗ в этой области. В статье рассмотрены основные направления деятельности Международной фармакопеи, порядок подбора текстов для включения в издание или их пересмотра, участие в борьбе с COVID-19 и сотрудничество с другими фармакопеями. Фармакопеи предлагают общедоступные стандарты (в виде текстов с требованиями и стандартных образцов), позволяющие обеспечить качество лекарственных средств за счет нормирования показателей, наиболее важных для безопасности и эффективности. Фармакопейные стандарты представлены методами анализа подлинности, чистоты и состава лекарственных средств, критериями приемлемости получаемых результатов, а также информацией о хранении, маркировке и производстве лекарственных средств. Наличие фармакопейных монографий существенно упрощает разработку воспроизведенных лекарственных средств согласно заданным минимальным стандартам качества, которым должен соответствовать препарат, чтобы можно было считать его сопоставимым с оригинальным препаратом (или несколькими) по безопасности, качеству и эффективности. Особенность Международной фармакопеи состоит в том, что основные усилия прикладываются к созданию монографий, актуальных для стран с низким и средним уровнем дохода, где может быть недостаточно ресурсов для разработки собственных фармакопей. В условиях глобализации лекарственные препараты, медицинские изделия и косметические средства часто импортируют из стран с разными стандартами регулирования и требованиями к медицинской продукции. При реагировании на чрезвычайные ситуации глобального характера в области общественного здравоохранения, такие как пандемия COVID-19, требуется оперативно проверять качество лекарственных средств и как можно быстрее с учетом интересов всех сторон обеспечить населению доступ к ним, что делает Международную фармакопею крайне необходимой.

Ключевые слова: Всемирная организация здравоохранения; Международная фармакопея; международные химические стандартные образцы; жизненно необходимые и важнейшие лекарственные препараты; преквалификация лекарственных средств

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Introduction

Since its inception more than 70 years ago, the World Health Organisation (WHO) has been developing and promoting international standards for pharmaceutical products, in support of efforts to increase access to quality-assured medicines for all, and to safeguard patients from substandard and falsified medicines. The International Pharmacopoeia is a key output of this work[1].

Unlike national (such as the British Pharmacopoeia, Indian Pharmacopoeia, Japanese Pharmacopoeia or United States Pharmacopoeia) or regional (such as the European Pharmacopoeia) pharmacopoeias, The International Pharmacopoeia has no legal status *per se*. WHO Member States are therefore free to adopt its provisions and to incorporate them into national legislation, either in part or in whole. *Figure 1* shows examples of WHO Member States that currently refer in their legislation or regulatory guidelines to The International Pharmacopoeia.

The first volume of The International Pharmacopoeia was published in 1951 and continues to be published with the aim of providing quality specifications for selected pharmaceutical products of small chemical entities, principally active pharmaceutical ingredients (APIs), finished pharmaceutical products (FPPs), excipients and radiopharmaceuticals. The International Pharmacopoeia's objective has evolved: from the "unification" of standards for medicines[2] to provision of a compendium of quality requirements for medicines that are deemed essential to meeting priority health care needs and often targeted at the high-burden diseases of low- and middle-income countries (LMIC). These medicines are either listed in the WHO Model List of Essential Medicines (EML)[3], in Invitations to Manufacturers to Submit an Expression of Interest for Product Evaluation to the WHO Prequalification Unit (EOIs)[4] and/or in WHO therapeutic guidelines.

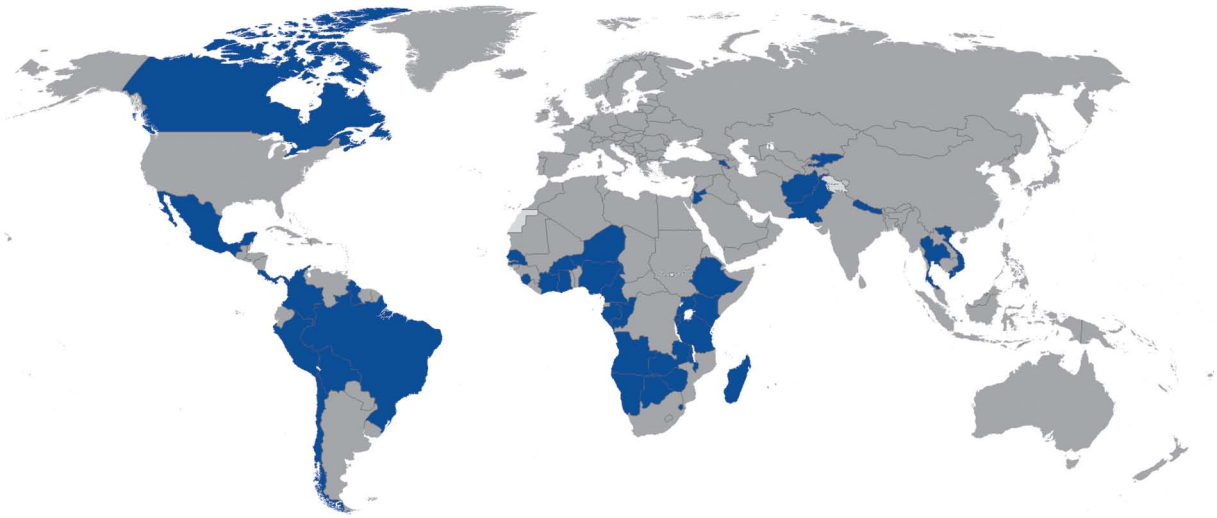

Fig. 1. *WHO Member States referring to The International Pharmacopoeia (highlighted in blue). The information is based on the Cortellis CMC[5] Intelligence database. Of the 114 Member States that shared this information, 44 accept The International Pharmacopoeia as a compendial standard*

Рис. 1. *Страны-члены Всемирной организации здравоохранения, в которых ссылаются на Международную фармакопею (выделены синим). Информация получена из базы данных Cortellis CMC[5] Intelligence. Международную фармакопею признают фармакопейным стандартом в 44 из 114 стран ВОЗ, которые поделились такой информацией*

[1] The International Pharmacopoeia. Geneva, World Health Organisation. https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/pharmacopoeia; https://apps.who.int/phint

[2] The unification of Pharmacopoeias. Interim report of the Technical Commission of Pharmacopoeial Experts. *Analyst*. 1946;71:494–5. https://doi.org/10.1039/AN946710494B

[3] WHO/MHP/HPS/EML/2021.02. World Health Organisation Model List of Essential Medicines — 22nd List, 2021. Geneva: World Health Organisation; 2021.

[4] FPPs & APIs Eligible for Prequalification. Geneva, World Health Organisation. https://extranet.who.int/pqweb/medicines/products-eligible-prequalification

[5] CMC: chemistry, manufacturing and controls. https://clarivate.com/products/biopharma/regulatory-compliance/chemistry-manufacturing-controls-intelligence-analysis/

WHO's work on norms and standards also serves as an important tool for Member States and other United Nations agencies, as well as for global health organisations such as the Clinton Health Access Initiative, public-private partnerships, non-governmental organisations such as Médecins Sans Frontières, and philanthropic organisations such as the Bill & Melinda Gates Foundation.

Value of pharmacopoeias

Facilitate production and registration. Pharmacopoeias help to streamline interaction between manufacturers and regulatory authorities: preparation and assessment of submissions is facilitated, and consistency in regulatory decision-making is supported. As a result, manufactures and regulators save time and resources. Moreover, in defining minimum quality standards that a medicine must meet in order to be considered safe and efficacious and of assured quality, a level playing field for all manufacturers producing that medicine is created. That is, the requirements to be met are the same for all manufacturers, which in turn enhances regulatory fairness, competition, and even local production of medicines[6].

Ensure safety of medicines. When healthcare professionals and patients use medicines that are known to adhere to pharmacopoeial quality standards, trust in their safety is generated. Using tests described in pharmacopoeias, independent laboratories, such as national quality control laboratories, can evaluate the quality of medicines without having to access the specifications and test methods of the manufacturers. Based on their test results, the responsible authorities can initiate swift actions to alert patients and healthcare professionals of quality defects or substandard and falsified medicines and initiate legal action if necessary.

Added value of The International Pharmacopoeia

Addresses the needs of LMIC. National and regional pharmacopoeias usually describe medicines that are registered or authorised for their markets. These medicines reflect the health priorities that apply for these countries. However, as many LMIC do not have sufficient resources to develop and maintain their own pharmacopoeias, there is a shortfall in monographs of particular relevance to those countries — for example, medicines for malaria, tuberculosis or neglected tropical diseases. The International Pharmacopoeia addresses this problem by focusing on these medicines. At the same time, it complements the pharmacopoeias of high-income countries with its focus on, for example, high-burden non-communicable diseases, such as diabetes and cardiovascular diseases.

Supports other key WHO activities. WHO prequalification of medicines is a service provided by WHO to assess the quality, safety and efficacy of medicines. Initiated in 2001 with a focus on medicines for treating HIV/AIDS, its scope was gradually extended to also cover medicines for tuberculosis, malaria, reproductive health, diarrhoeal disease, hepatitis B and C, infections in newborn and young infants and childhood pneumonia, influenza, neglected tropical diseases, reproductive health, and, most recently, selected biotherapeutic products and COVID-19. WHO's global norms and standards for medicines quality and safety, including the monographs of The International Pharmacopoeia[7], underpin medicines prequalification.

WHO's efforts to combat substandard and falsified medicines, and to increase local production, are also supported by The International Pharmacopoeia since for any medicine that is being tested in order to ascertain its identity, purity and content, or for which production is being enhanced, clear definition of its targeted quality attributes and provision of analytical methods to test for them are vital.

Development process of monographs for inclusion in The International Pharmacopoeia

Monographs for The International Pharmacopoeia are developed through an open and transparent process and in consultation with an international panel of experts, WHO Collaborating Centres and collaborating

[6] White Paper for the WHO International Meeting of World Pharmacopoeias, Value of Pharmacopoeial Standards for Access to Quality Medicines. Geneva; World Health Organisation. https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/value-of-pharm-stds-updated-final-oct-2020.pdf?sfvrsn=2d4e5052_4

[7] World Health Organisation Prequalification. Geneva; World Health Organisation. https://extranet.who.int/pqweb/

laboratories. The procedure is governed by conflict of interest and confidentiality rules and recognises international standards, including Good Pharmacopoeial Practices[8].

The methods and associated limits prescribed in monographs are usually developed and validated by manufacturers and authorised by regulatory authorities or the WHO Prequalification of Medicines. Emphasis is placed on analytical techniques that are globally applicable and can also be performed in resource-limited settings and remote areas. To this end, users are provided with different options for the control of products, ranging from well-established and robust wet chemistry tests or thin-layer chromatography, to advanced instrumental methods, like infrared spectroscopy and High Performance Liquid Chromatography. This enables them to select the methods that are available and applicable in the environments in which they operate.

For the quantification of pharmaceutical substances, absolute methods like titrations and the use of the absorptivity in ultraviolet and visible absorption spectrophotometry, are preferred to relative methods. In these cases, the specificity of the assay is conferred by the combination with other tests in the monograph.

Following ICH Q6A, it is not considered necessary to test finished products for synthesis impurities which are controlled in the active API and are not degradation products[9]. Wherever possible, The International Pharmacopoeia provides the same methods for the test for related substances in FPPs and in the corresponding API(s), so that users can evaluate whether an API of compendial quality was used in the manufacture of the FPP. Since for post-market surveillance of medicines, recourse to samples of API is often not possible, this is clearly an asset.

The provisions of each draft monograph are verified by laboratory investigations, including analysis of authorised samples from different regions of the world. Based on the results of the investigations, the provisions may be modified or optimised.

Feedback on draft monographs is solicited from stakeholders, including WHO Member States, national medicine regulatory authorities, other pharmacopoeias and other UN organisations, manufacturers and their associations, and quality control laboratories around the world. Draft monographs are also made available for consultation by being posted on the website[10]. Comments received are reviewed with those experts who were involved in setting up the requirements. If needed, additional laboratory investigations may be organised, and the monographs revised to take new results into account. Once any revision has been completed, the draft monographs, associated laboratory reports and a compilation of all comments received, are submitted to the Expert Committee on Specifications for Pharmaceutical Products (ECSPP) for information, discussion and/or possible adoption, depending on the maturity of the text. If adopted, the monograph is published in the next edition of The International Pharmacopoeia.

Work plan

To best meet the needs and expectations of WHO Member States and WHO programmes, a survey is performed every two years to identify medicines that are considered to be a priority, but for which no public quality standard has yet been included in any of the major pharmacopoeias. FPPs listed on the current EML[11] or included in a WHO EOI[12]

[8] Procedure for the elaboration, revision and omission of monographs and other texts for The International Pharmacopoeia. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: Fifty-fourth report. Geneva: World Health Organisation; 2020: Annex 1. https://www.who.int/publications/i/item/978-92-4-000182-4

[9] ICH Harmonised Tripartite Guideline; Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances Q6A. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 1999. https://database.ich.org/sites/default/files/Q6A%20Guideline.pdf

[10] Monographs and general texts under review/revision for inclusion in The International Pharmacopoeia. Geneva; World Health Organisation. https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation

[11] WHO/MHP/HPS/EML/2021.02. World Health Organisation Model List of Essential Medicines — 22nd List, 2021. Geneva: World Health Organisation; 2021.

[12] FPPs & APIs Eligible for Prequalification. Geneva, World Health Organisation. https://extranet.who.int/pqweb/medicines/products-eligible-prequalification

are compared with those described in the most recent editions of the four pharmacopoeias with finished product monographs and recognised by the Prequalification Unit: the British, International, Japanese and United States Pharmacopoeias. The latest survey, performed after publication of the 21st EML, revealed that of the 691 medicines that are mentioned in the EML, or in a relevant EOI, 186 (27%) currently lack a public standard and/or are not included in one or more of the four mentioned pharmacopoeias. Of these 186 medicines, 20% are antiviral medicines and 19% to anti-tuberculosis medicines.

The International Pharmacopoeia has been focusing on medicines that are eligible for product evaluation for prequalification ever since the launch of WHO medicines prequalification in 2001. It currently includes monographs for about 30% to 60% of these medicines, depending on the pharmacological section to which they belong (*see Table 1*). Well-covered medicines include, for example, medicines for tropical diseases (almost 60% covered) and antimalarial medicines (about 50% covered). Medicines for therapeutic areas that so far are not eligible for prequalification, or to a limited extent only, feature to a lesser extent (for example, cancer medicines or insulins).

The International Pharmacopoeia will continue to serve the WHO medicines prequalification: 46 of the 186 medicines mentioned above are included on the 21st EML, eligible for prequalification, mentioned in a relevant EOI, lack a public standard, and not covered by The International Pharmacopoeia. These medicines are considered a priority for the elaboration of monographs as per the 2022–23 work plan:

1) Abacavir and lamivudine dispersible tablets
2) Abacavir dispersible tablets
3) Amodiaquine dispersible tablets
4) Amphotericin b liposomal complex for injection
5) Artemether and lumefantrine dispersible tablets
6) Artenimol and piperaquine phosphate tablets
7) Artesunate and amodiaquine tablets
8) Artesunate and mefloquine tablets
9) Artesunate and pyronaridine tablets
10) Artesunate rectal capsules
11) Atazanavir and ritonavir tablets
12) Baricitinib tablets
13) Bedaquiline tablets
14) Carbetocin injection
15) Clofazimine tablets
16) Darunavir tablets
17) Dasabuvir tablets
18) Delamanid tablets
19) Dolutegravir tablets
20) Estradiol cypionate and medroxyprogesterone acetate injection
21) Ethambutol dispersible tablets
22) Ethionamide dispersible tablets
23) Fexinidazole tablets
24) Isoniazid dispersible tablets
25) Lamivudine, tenofovir disoproxil fumarate and dolutegravir tablets
26) Ledipasvir and sofosbuvir tablets
27) Levofloxacin dispersible tablets
28) Linezolid dispersible tablets
29) Linezolid powder for suspension
30) Linezolid tablets
31) Mifepristone tablets
32) Miltefosine capsules
33) Molnupiravir capsules
34) Moxifloxacin dispersible tablets
35) Nirmatrelvir tablets
36) Norethisterone enantate injection
37) Ombitasvir, paritaprevir and ritonavir tablets
38) Oseltamivir powder for oral suspension
39) P-Aminosalicylic acid granules for oral solution
40) Paromomycin sulfate for intramuscular injection
41) Pyrazinamide dispersible tablets
42) Pyrimethamine and sulfadoxine dispersible tablets
43) Rifabutin tablets
44) Rifapentine tablets
45) Sofosbuvir and velpatasvir tablets
46) Ulipristal acetate tablets

Table 1. *Percentage coverage of monographs in The International Pharmacopoeia per pharmacological section of the Essential Medicines List**

Таблица 1. *Доля лекарственных средств, охваченных монографиями Международной фармакопеи, в соответствии с разделами Примерного перечня основных лекарственных средств ВОЗ**

Раздел *Section*	**Имеющиеся монографии, шт.** *Existing Monographs, pieces*	**Планируемые монографии**, шт.** *Candidate Monographs**, pieces*	**Удовлетворенная потребность в монографиях, %** *Coverage, % (overall)*
Лекарственные средства, применяемые для охраны репродуктивного здоровья и при оказании помощи новорожденным, детям и подросткам *Medicines for maternal, newborn, child and adolescent health*	14	24	37
Противомалярийные лекарственные средства *Antimalarial medicines*	17	17	50
Противовирусные лекарственные средства, включая антиретровирусные *Antiviral medicines including antiretrovirals*	27	51	35
Противотуберкулезные лекарственные средства *Antituberculosis medicines*	19	47	29
Лекарственные средства для лечения тропических болезней *Medicines for tropical diseases*	23	16	59
Лекарственные средства, применяемые при хронических заболеваниях, в том числе при психических расстройствах *Medicines for chronic diseases and for mental health*	6	104	5
Прочие противоинфекционные лекарственные средства *Other medicines for infectious diseases*	17	61	22
Лекарственные средства, применяемые при заболеваниях крови *Haemopathy medicines*	0	7	0
Лекарственные средства, действующие на желудочно-кишечный тракт *Gastrointestinal medicines*	0	20	0
Лекарственные средства, применяемые для анестезии, уменьшения боли и в паллиативной терапии *Medicines for anaesthesia, pain and palliative care*	7	33	17
Иммуномодуляторы и противоопухолевые лекарственные средства *Immunomodulators and antineoplastics*	2	67	3
Лекарственные средства, применяемые при нарушениях питания *Medicines for nutrition disorders*	2	30	6
Противоаллергические лекарственные средства и средства, применяемые при анафилактических реакциях *Antiallergics and medicines used in anaphylaxis*	0	2	0
Антидоты и другие вещества, применяемые при отравлениях *Antidotes and other substances used in poisonings*	1	12	8
Прочие лекарственные средства, применяемые при нарушениях со стороны эндокринной системы *Other medicines for endocrine diseases*	0	8	0

Table 1 (continued)

Продолжение таблицы 1

Раздел *Section*	**Имеющиеся монографии, шт.** *Existing Monographs, pieces*	**Планируемые монографии**, шт.** *Candidate Monographs**, pieces*	**Удовлетворенная потребность в монографиях, %** *Coverage, % (overall)*
Миорелаксанты и противоревматические препараты, модифицирующие течение болезни *Muscle relaxants and disease-modifying anti-rheumatic medicines*	0	9	0
Офтальмологические и дерматологические лекарственные средства *Ophthalmological and dermatological medicines*	0	40	0
Лекарственные средства, применяемые в связи с COVID-19 *COVID-19 related medicines*	2	6	25
Всего / *Total*	137	554	20

* *Для удобства некоторые разделы EML в таблице объединены в более общие группы.*
** *Монографии на лекарственные средства, вошедшие в Примерный перечень основных лекарственных средств ВОЗ (Essential Medicines List, EML) или упомянутые в соответствующих Приглашениях производителей к выражению заинтересованности в оценке группой ВОЗ по преквалификации (Expression of Interest, EOI), которых пока нет в Международной фармакопее.*
* *For simplicity, some of the sections in the Essential Medicines List have been subsumed under overarching groups.*
** *Candidate monographs describe medicines that are either mentioned in the Essential Medicines List or in a relevant Expression of Interest and for which a monograph in The International Pharmacopoeia has not yet been developed.*

Response to the COVID-19 pandemic

As of 6 February 2022, WHO had reported over 392 million confirmed cases of SARS-Co-V-2 and over 5.7 million deaths[13]. The International Pharmacopoeia is supporting efforts to ensure the quality and safety of COVID-19 therapeutics mentioned in the guideline Therapeutics and COVID-19: living guideline[14] and to facilitate their manufacture, registration and procurement through development of new or revision of existing monographs. Given the focus of The International Pharmacopoeia on small chemical entities that can be fully characterised by physicochemical means alone as opposed to biological products which require some form of bioassay, new monographs on remdesivir and molnupiravir were developed and the existing monograph on oxygen was revised. Monographs on systemic corticosteroids, like dexamethasone phosphate, had been included previously. The described test methods, together with the corresponding limits, continue to reflect the current state of the art and science. Further monographs are planned, following the evaluation of the corresponding therapeutics by the independent panel of experts advising WHO's Guideline Development Group (GDG).

Remdesivir. Remdesivir is a novel adenosine monophosphoramidate analogue prodrug which is metabolised to an active tri-phosphate form that inhibits viral RNA synthesis. Remdesivir has *in vitro* and *in vivo* antiviral activity against several viruses, including SARS-CoV-2. In March 2020, a large, international, open-label, randomised trial was initiated to evaluate the effect of remdesivir on the mortality of hospitalised patients[15]. Based on this and other studies, the GDG made a conditional recommendation against using remdesivir for treatment of hospitalised patients with COVID-19. The GDG considered that evidence that remdesivir improved outcomes that matter to patients, such as reduced mortality, need for mechanical ventilation and time to clinical improvement, was

[13] Weekly epidemiological update on COVID-19. Geneva; World Health Organisation. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---8-february-2022
[14] Therapeutics and COVID-19, Living Guideline. Geneva; World Health Organisation. https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1
[15] WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19 — interim WHO Solidarity trial results. *New Eng J Med.* 2021;384(6):497–511. https://doi.org/10.1056/nejmoa2023184

insufficient for recommending its use. However, the conditional recommendation against the use of remdesivir has been recently reviewed[16]. As remdesivir containing medicines are authorised in several countries, monographs on remdesivir and remdesivir intravenous infusion were developed to enable national and other quality control laboratories to test for the quality of these products, thereby safeguarding patients from substandard and falsified products. In fact, in August 2021, the WHO Incidents and Substandard and Falsified Medicines team reported that falsified remdesivir was identified in WHO region of the Americas[17].

The remdesivir monographs were drafted based on information submitted by manufacturers and available in the public domain, distributed twice for public consultation and adopted at the 55th meeting of the Expert Committee on Specifications for Pharmaceutical Preparations[18].

Molnupiravir. Molnupiravir, a prodrug of the nucleoside analogue β-D-N4-hydroxycytidine, was reported to reduce the risk of hospitalisation in patients with mild to moderate COVID-19. The GDG issued a conditional recommendation for use of molnupiravir, suggesting treatment of patients at highest risk of hospitalisation and excluding pregnant or breastfeeding women and children[19]. Molnupiravir capsules were also included in the 7th Invitation to Manufacturers of Therapeutics against COVID-19 to submit an EOI for product evaluation to the WHO Prequalification Unit. Draft monographs on molnupiravir and molnupiravir capsules for inclusion in The International Pharmacopoeia were drafted and distributed for public consultation recently[20].

Pharmacopoeias respect the intellectual property of manufacturers and recognise the importance of maintaining the confidentiality of proprietary third-party information. Thus development of a monograph is generally not initiated until the medicine concerned has reached the end of its exclusivity in its jurisdictions. As patents are granted for countries and regions individually under the jurisdiction of national/regional patent laws, worldwide patents do not exist. That said, elaboration of a monograph for inclusion in The International Pharmacopoeia can start as soon as manufacturers who lawfully produce the corresponding products — for example as the originator, through cooperation with him and/or the use of TRIPS flexibilities — provide the necessary information. This explains why WHO could develop monographs for remdesivir and molnupiravir so quickly, as part of its response to the COVID-19 pandemic.

Medicinal oxygen. Oxygen is an essential medicine and often the sole means for treating diseases that affect the respiratory tract — such as COVID-19 and pneumonia. It is also essential for surgery and managing trauma. Oxygen is produced by liquefaction of air in a large-scale industrial process or by pressure/vacuum swing adsorption (PSA or VSA) , often at hospitals, whereby ambient air is conducted over molecular sieves or other materials which adsorb certain components of the air, in particular nitrogen and carbon dioxide, and enrich the oxygen.

In the course of the COVID-19 pandemic, oxygen shortages were severe and resulted in countless preventable deaths, in particular in LMIC. In revising the monograph on oxygen, WHO mitigated this critical situation, and increased universal and equitable access to medicinal oxygen. The revised monograph clarified that both oxygen qualities — oxygen produced by liquefaction of ambient air and oxygen generated by PSA or VSA — can be administered safely to patients. The monograph also puts an end to discussions as to whether industrial oxygen can be used for human application. Only medicinal oxygen of defined quality, which has been tested and meets

[16] Therapeutics and COVID-19: Living guideline. Geneva; World Health Organisation. https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1

[17] Medical Product Alert No. 4/2021: Falsified remdesivir. Geneva, World Health Organisation. https://www.who.int/news/item/13-08-2021-medical-product-alert-n-4-2021-falsified-remdesivir

[18] WHO Expert Committee on Specifications for Pharmaceutical Preparations: 55th report. Geneva: World Health Organisation; 2021. WHO Technical Report Series, No. 1033. https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

[19] Therapeutics and COVID-19: Living guideline. Geneva; World Health Organisation. https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1

[20] Monographs and general texts under review/revision for inclusion in The International Pharmacopoeia. Geneva; World Health Organisation. https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation

the authorised specifications for its identity, purity and content, and which was produced, and is stored and distributed in adherence with good practices, should reach the patient. Uncertainties regarding the purity and content of industrial oxygen, the possible occurrence of particulate and microbial contamination, and production, storage and distribution processes that may not be planned, performed and controlled in accordance with good practices that reflect health care needs, can result in unacceptable risks for patients and therefore should not be used for human application[21].

The different versions of the monograph were discussed at various internal and external meetings and sent out for public consultation twice. An interim version was published on the website of WHO[22] and submitted to the 56th meeting of the ECSPP in April 2022 for possible adoption.

International Chemical Reference Substances

Purpose of ICRS. International Chemical Reference Substances (ICRS) are primary chemical reference substances for use in physical and chemical tests and assays described in The International Pharmacopoeia or in other documents adopted by the ECSPP.

Based on results obtained from comparison with ICRS, medicines can be released to the market or tested for compliance when applying tests described in The International Pharmacopoeia. In particular, ICRS are used to ascertain the identity of pharmaceutical substances and impurities, to determine the assay of APIs and FPPs, to identify and quantify impurities in tests for related substances, to verify the suitability of test methods, and to calibrate analytical instruments. They serve as a benchmark and ensure the accuracy of methods and instruments and comparability of analytical results.

ICRS are established for a specific purpose — namely, the use described in The International Pharmacopoeia and in the leaflet enclosed with the standard when distributed. For any other use of the ICRS, the responsibility for assessing the suitability of the standard rests with the user or with the authority that has prescribed its use. This includes, for instance, their use in tests and assays not described in The International Pharmacopoeia. (e.g., validation of alternative analytical methods).

Since 2010, ICRS have been established, stored and distributed by the European Directorate for the Quality of Medicines & Healthcare (EDQM) on the advice of and approved and adopted by the ECSPP. So far, more than 250 primary reference substances have been established. ICRS are a reliable, cost-effective alternative to developing own reference standards. The following list includes recently established ICRS:

1) Levamisole hydrochloride ICRS 1
2) Amodiaquine hydrochloride ICRS 2
3) Ciprofloxacin hydrochloride ICRS 2
4) Ciprofloxacin impurity A ICRS 1
5) alpha-Artemether ICRS 2
6) Daclatasvir dihydrochloride ICRS 1
7) Daclatasvir for system suitability ICRS 1
8) Daclatasvir for peak identification ICRS 1
9) Carbamazepine ICRS 2
10) Dexamethasone phosphate for assay ICRS 1

Production and characterisation of ICRS. The operations related to the establishment, storage and distribution of ICRS are carried out according to relevant norms and guidelines, including the WHO General guidelines for the establishment, maintenance and distribution of chemical reference substances[23].

Generally, the candidate material for the establishment of ICRS is a batch of normal production quality. In order to establish the reference substance, all relevant quality attributes of the material are characterised. Identity is confirmed and purity is determined, usually based on results obtained using the methods described in the respective monographs. Additional analytical

[21] Oxygen. Geneva; World Health Organisation. https://www.who.int/health-topics/oxygen#tab=tab_1
[22] Monographs and general texts under review/revision for inclusion in The International Pharmacopoeia. Geneva; World Health Organisation. https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation
[23] WHO general guidelines for the establishment, maintenance and distribution of chemical reference substances. Geneva; World Health Organisation: 2007: Annex 3. WHO Technical Report Series, No. 943. https://www.who.int/publications/m/item/who-general-guidelines-for-the-establishment-maintenance-and-distribution-of-chemical-reference-substances---trs-943---annex-3

techniques are employed to elucidate the structure and configuration of ICRS, if need be (e.g. NMR, exact mass measurement and chiral HPLC). Absolute methods (for example, volumetric titrations, differential scanning calorimetry, qNMR) are used to complement and verify the results of relative (mostly chromatographic) methods. The extent of testing and the number of laboratories involved depend on the quality of the candidate, its intended use and purity.

For quantitative standards intended for use in assays (requiring the assignment of a content), the cumulative percentage of all components (impurities and main component) should yield 100% (mass balance approach). The contributions of other constituents (i.e. organic and inorganic impurities, water and residual solvents) that exceed a predefined threshold are determined in inter-laboratory studies (usually performed by 5 laboratories).

In addition to the purity of the candidate material, the content ultimately assigned to an ICRS depends on the selectivity of the chromatographic method for which the substance will serve as a reference. If the reference substance is intended to be used with a method that has the same selectivity as the method used to determine its purity, the content of the ICRS is applicable. If, however, the intended method is less discriminative, the content of impurities that cannot be discriminated from the detector response of the parent compound needs to be accounted for and the assigned value needs to be corrected for that.

ICRS are stored, shipped and distributed under conditions that ensure their continuous fitness for use. EDQM monitors the stability of ICRS by regular re-examination, the frequency and extent of which are based on data available on the stability of the ICRS and its intended use. Material that has deteriorated is replaced. The list of valid batches is accessible in the on-line ICRS catalogue[24].

Rational use of ICRS. The specifications and test procedures of The International Pharmacopoeia are developed to be applicable in all WHO Member States wishing to implement them. Procuring the necessary reference substances may, however, be difficult in certain areas of the world due to delays in their delivery or the costs of transport. The International Pharmacopoeia therefore endeavours to reduce the number of reference substances required to perform the prescribed analytical tests by, for example:

- *in situ* preparation of impurities for identification of related substances/impurities;
- provision of International Infrared Reference Spectra for identification by Infrared Spectroscopy;
- quantification of impurities by comparing their detector responses with the response of the parent compound in a diluted sample solution, together with the establishment of correction factors to compensate for differences in the responses of impurities and related parent compounds; and
- favouring absolute methods, like titrations and ultraviolet spectrophotometry using absorptivity values for assays of APIs, since these do not require reference substances.

These strategies are, however, applied only when, during the elaboration of the monograph, evidence has been obtained that demonstrates that the intended measures neither compromise the quality of the analytical results nor the capacity of the tests to conclusively demonstrate conformance to the applicable standards.

Collaboration with other pharmacopoeias

Diversity in the standards describing the quality of essential medicines may impede universal and equitable access to these medicines. In 2012, WHO therefore brought together representatives of pharmacopoeias at the first International Meeting of World Pharmacopoeias (IMWP) in Geneva, to foster collaboration among pharmacopoeias and to discuss how to support harmonisation of compendial standards. During the 12 meetings that followed, the following were jointly developed:

- WHO Good Pharmacopoeial Practices, which describe principles for the design, development and maintenance of pharmacopoeial standards, with the ultimate goal of harmonisation[25];

[24] WHO International Chemical Reference Substances (ICRS): Purposes & Use. Strasbourg. European Directorate for the Quality of Medicines & HealthCare. https://www.edqm.eu/en/WHO-ICRS-Reference-Substances-1393.html

[25] WHO Good Pharmacopoeial Practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: 50th report. Geneva; World Health Organisation; 2016. Annex 1, WHO Technical Report Series 996. https://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_web.pdf

- a White Paper on the value of public standards for universal access to quality-assured medicines[26];

Pharmacopoeias also agreed on a Pharmacopoeial Alert System, to facilitate rapid exchange of information between pharmacopoeias during public health emergencies. The system was first activated in 2020 with the advent of the COVID-19 pandemic, to rapidly exchange information on relevant activities and support the global public health response. During 10 virtual meetings of the Pharmacopoeial Alert System, held in 2020 and 2021, the following were established:

- a dashboard on the WHO/IMWP website that lists monographs for medicines currently under investigation for the treatment of COVID-19 and which provides a quick overview as to which pharmacopoeia contains which monographs[27] and
- the IMWP monographs on favipiravir and favipiravir tablets which were developed by the Japanese Pharmacopoeia with support from other pharmacopoeias[28].

The monographs on favipiravir and favipiravir tablets are the first IMWP monographs to be established which are neither legally binding, nor intended to become legally binding. IMWP monographs are intended solely to be used as analytical tools by, for example, those official control laboratories, who are involved in the fight against falsified and substandard products.

Conclusion

In focusing on medicines relevant for LMIC, The International Pharmacopoeia complements other pharmacopoeias, like the British, European, Japanese and United States Pharmacopoeias, which focus more on the quality of medicines and APIs used and authorised in high-income countries. The compendium supports and underpins activities of several WHO programmes, including Prequalification of Medicines, Local Production & Assistance, Incidents and Substandard and Falsified Medicines. It helps to ensure that all patients everywhere receive medicines that are effective, safe and quality assured.

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[26] White Paper for the WHO International Meeting of World Pharmacopoeias, Value of Pharmacopoeial Standards for Access to Quality Medicines. Geneva; World Health Organisation. https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/value-of-pharm-stds-updated-final-oct-2020.pdf?sfvrsn=2d4e5052_4

[27] International Meetings of World Pharmacopoeias. Geneva; World Health Organisation. https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/pharmacopoeia/IMWP

[28] IMWP Monographs on Favipiravir and on Favipiravir tablets. Geneva; World Health Organisation. https://www.who.int/publications/m/item/imwp-monographs-on-favipiravir-and-on-favipiravir-tablets

AUTHORS / ОБ АВТОРАХ

Herbert Schmidt, Ph. D.
ORCID: https://orcid.org/0000-0002-7987-6384
schmidth@who.int
Jacqueline Sawyer
ORCID: https://orcid.org/0000-0001-9037-2438
sawyerj@who.int
Kaouther Zribi, Ph. D.
ORCID: https://orcid.org/0000-0002-6045-0914
kaouthar_z@yahoo.fr
Remmelt van der Werf, Ph. D.
ORCID: https://orcid.org/0000-0002-7987-6384
remmelt.vanderwerf@edqm.eu

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Герберт Шмидт, Ph. D.
ORCID: https://orcid.org/0000-0002-7987-6384
schmidth@who.int
Жаклин Сойер
ORCID: https://orcid.org/0000-0001-9037-2438
sawyerj@who.int
Каутер Зриби, Ph. D.
ORCID: https://orcid.org/0000-0002-6045-0914
kaouthar_z@yahoo.fr
Реммельт ван дер Верф, Ph. D.
ORCID: https://orcid.org/0000-0002-8619-5878
remmelt.vanderwerf@edqm.eu

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