Overall programme review of the global strategy and plan of action on public health, innovation and intellectual property

Report of the review panel

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World Health Organization

Contents

Acknowledgements

Interviews
The review panel received valuable contributions from Member States, United Nations specialized agencies, governmental and nongovernmental organizations and individuals. In particular, the panel wishes to thank the following individuals who agreed to be interviewed:

Chi Pharmaceuticals Limited: Orakwue Ikenna, Head, Public Health & Institutions.
Johnson & Johnson Global Public Health: Jens Bitsch-Norhave, Head, Business Development & Licensing; Karen Grosser, Vice President, Infectious Disease and Vaccine Therapeutic Area; Adrian Thomas, Vice President, Global Head Health Economics & Market Access Medical Devices.
Medicines Patent Pool: Esteban Burrone, Head of Policy.
Organisation for Economic Co-operation and Development (OECD): Valerie Paris, Senior Policy Analyst, Health Division.
Otsuka Pharmaceutical: Raj Gupta, Senior Director; Marc Destito, Communications Director, Global tuberculosis (TB) program.
Takeda Pharmaceutical: Ali Alloueche, Head, Technology Strategy & Alliance Management.
United Nations Conference on Trade and Development (UNCTAD): Christoph Spennemann, Legal Officer and Officer-in-Charge, Intellectual Property Unit.
Walter Reed Army Institute of Research (WRAIR): Colonel Nelson Michael, Director of the US Military HIV Research Program (MHRP).
World Trade Organization (WTO): Roger Kampf, Counsellor, Intellectual Property, Government Procurement and Competition Division.

Survey
The review panel conducted an on-line survey to seek input on elements of the global strategy and plan of action on public health, innovation and intellectual property and the way forward. The panel wishes to thank the following stakeholders for submitting responses for the panel's consideration:

Member States: Armenia, Australia, Austria, Bahrain, Brazil, Côte d'Ivoire, Czech Republic, Estonia, Georgia, Iraq, Japan, Latvia, Mexico, Montenegro, Netherlands, Peru, Switzerland, United Kingdom of Great Britain and Northern Ireland, United States of America, Zambia.

Other Stakeholders: Biotechnology Innovation Organization, Boston University School of Public Health, Developing Countries Vaccine Manufactures Network, Drugs for Neglected Diseases initiative, European Federation of Pharmaceutical Industries and Associations, Global Alliance for TB Drug Development, Global Health Technologies Coalition, Health Action International, High Lantern Group, Imperial College of London, International Federation of Pharmaceutical Manufacturers and Associations, Knowledge Ecology International, Medicines Patent Pool, Médecins Sans Frontières (MSF Access Campaign), PT Bio Farma, South Centre, The European Consumers Organization, The South American Institute of Government in Health, Third World Network, United Nations Conference on Trade and Development, Universities Allied for Essential Medicines, University of KwaZulu-Natal, Utrecht University, Wellcome Trust, World Trade Organization, Zydus Cadila.

Open Session
To engage further with Member States and stakeholders, the review panel called an open session. It wishes to thank the following stakeholders for their participation:

Member States: Australia, Belgium, Brazil, Ecuador, EU Delegation, France, Germany, Japan, Malta (remote), Mexico (remote), Mozambique, Netherlands, Peru, Switzerland, Thailand, United Kingdom of Great Britain and Northern Ireland, United States of America, Zambia.

Other Stakeholders: Drugs for Neglected Tropical Diseases initiative, Health Action International, International Federation of Pharmaceutical Manufacturers and Associations, International

Pharmaceutical Federation, Knowledge Ecology International, Médecins sans Frontières, Medicines Patent Pool, OXFAM (remote), Bio Farma Indonesia (remote), South Centre, Third World Network (remote), United Nations Conference on Trade and Development, Universities Allied for Essential Medicines, World Trade Organization.

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Preface

The global strategy and plan of action on public health, innovation and intellectual property (GSPA-PHI) was the culmination of several years of work in WHO and a prolonged negotiation between Member States, to promote new thinking on innovation and access to medicines. It sets out an important vision and a policy framework which has the aim of transforming health research and development (R&D) priorities to reflect developing country needs and of facilitating access to medicines and other health products in those countries.

In resolution WHA68.18, Member States requested the WHO Director-General to establish a panel of 18 experts to review the global strategy and plan of action on public health, innovation and intellectual property. The purpose of the review was to complement the comprehensive evaluation commissioned by the WHO Secretariat with a more policy-oriented, forward-looking perspective. Our review has confirmed that while there have been some positive developments since 2008, the fundamental concerns that justified the development of the GSPA-PHI remain.

Research and development is still not sufficiently directed at health products for diseases that mainly affect developing countries. Resources devoted to R&D on these diseases have not sustainably increased. There is evidence of progress for some diseases but for many diseases we still lack the tools and financial resources necessary if we are, for example, to meet the health targets set in the Sustainable Development Goals. And lack of access to health products remains an acute problem for millions of people, in spite of considerable achievements in some areas such as expanding treatment coverage for HIV. Improving access to medicines and other health products will be an essential component in moving towards universal health coverage.

There are also new challenges arising from the changing burden of disease as populations age and become rapidly urbanized; from the growing recognition of the dangers posed by antimicrobial resistance, and the threats from disease outbreaks. New treatments, particularly for cancers or hepatitis, can be prohibitively expensive, even in relation to the resources available in developed countries. Some new drugs come onto market without significant benefits to survival or quality of life, provoking debate about the need for a more appropriate balance between R&D versus marketing investments.

The GSPA-PHI is an ambitious framework, but its 108 action points are too many and lacking in precision. It has proved difficult to monitor progress. Too little effort has been devoted by all stakeholders to pursuing its implementation. The low awareness of the GSPA-PHI revealed by WHO's own evaluation is symptomatic of its lack of significant overall impact.

Our panel discussed all these issues and inevitably, there were some differences in view and emphasis. We therefore focused our efforts on obtaining the best possible consensus amongst our fellow panel members. We all decided that we needed to produce a shorter list of more focused and realistic priority actions directed principally at the WHO Secretariat and its Member States with measurable indicators. Our emphasis was as much on implementable and concrete actions as on grand ambitions. Thus, we focus on institutional mechanisms to identify R&D gaps and priorities; promoting improved collaboration, coordination in R&D and transparency in R&D costs; strengthening R&D capacity; promoting technology transfer; intellectual property measures that include encouraging the use of TRIPS flexibilities, greater transparency in patenting and licensing, and expanding patent pooling and a variety of measures to promote delivery of health care and access to health products.

However, we have retained the central grand ambition, which motivated the GSPA-PHI, that more resources need to be found for R&D for diseases mainly affecting developing countries as well as for

promoting access in line with the goal of universal health coverage. That is why we propose countries commit to more than double their financing to basic and applied research relevant to the health needs of developing countries, and continue to pursue new R&D models that reconcile the need to generate resources for R&D with the facilitation of access.

We were asked only to make recommendations for improving the implementation of the GSPA-PHI from now to 2022 when its current mandate expires. We are conscious that 2022 is not far away. Member States need to start considering now what should follow to address the objectives of the GSPA-PHI up to 2030 and beyond.

We were honoured to be asked to chair the review of the global strategy and plan of action on public health, innovation and intellectual property and would like to thank our fellow Panel Members for stimulating discussions and wise counsel. The WHO Secretariat did excellent work in supporting us. In particular we would like to thank the many Member States and other stakeholders who provided us with their views on the future shape of the GSPA-PHI.

Professor Claudia Chamas

Professor Elias Mossialos

Co-Chairs

Review panel members

Dr Chutima Akaleephan, former Programme Manager and Senior Researcher, International Health Policy Programme, Ministry of Public Health, Thailand

Dr Salah Nasser Al Muzahmi, Director of Research and Development Indicators Department, Statistical Centre for the Cooperation Council for the Arab Countries of the Gulf, Oman

Dr Ibrahim A. Aljuffali, Advisor to the Minister of Health, Saudi Arabia

Dr Christine Årdal, Senior Advisor, Institute of Public Health, Norway

Dr Shabir Banoo, Chief Technical Specialist, Pharmaceutical Policy and Programmes, Right to Care, South Africa

Professor Claudia Chamas, Centre for Technological Development in Health, Oswaldo Cruz Foundation, Brazil

Professor Carlos Correa, Director, Centre for Interdisciplinary Studies on Industrial Property and Economics and of the Post-graduate Course on Intellectual Property at the Law Faculty, University of Buenos Aires, Argentina

Professor Jonathan Craig, Associate Dean and Chair, Research Training Committee, University of Sydney, Sydney School of Public Health, Australia

Professor Yan Guo, Professor, School of Public Health, Peking University Health Science Centre, China

Dr Martha Gyansa-Lutterodt, Director of Pharmaceutical Services and Chief Pharmacist, Ghana

Dr Harimat Hendrawan, Deputy Director, Health Resources, Centre of Health Resources and Services Research and Development, Ministry of Health, Indonesia

Mr Erik Iverson, Managing Director, Wisconsin Alumni Research Foundation, United States of America

Dr Bita Mesgarpour, Director, National and International Affairs, National Institute for Medical Research Development, Islamic Republic of Iran

Dr Jaime C. Montoya, Executive Director, Department of Science and Technology, Council for Health Research and Development, Philippines

Professor Elias Mossialos, London School of Economics and Political Science and Imperial College London, United Kingdom

Professor Ibrahima Seck, Technical Adviser, Minister of Health, Senegal

Dr Soumya Swaminathan,[1] Secretary, Government of India, Department of Health Research, Ministry of Health and Family Welfare, and Director General, Indian Council of Medical Research, India

Professor Yazdan Yazdanpanah, Head, Infectious Disease Department, Bichat Claude Bernard Hospital, Head, INSERM team on decision analysis in infectious diseases, Professor of Medicine, Paris Diderot University, France.

[1] Now, Deputy Director-General, WHO headquarters, Geneva, Switzerland

A. Background

Terms of reference

Overall programme review of the global strategy and plan of action on public health, innovation and intellectual property

The Executive Board decided to approve the terms of reference of the overall programme review of the global strategy and plan of action on public health, innovation and intellectual property, set out in the Annex to this decision, and also to request the Secretariat to develop an indication of funding requirements and possible sources of the implementation costs of the recommendations of the programme review, and present these to the Seventy-first World Health Assembly in 2018 through the Executive Board at its 142nd session.

Annex

Terms of reference of the overall programme review

1. As directed in resolution WHA68.18 (2015), the overall programme review, as distinct from the evaluation, will be a more policy-oriented, forward-looking exercise. The expert review panel's conclusions should identify areas of convergence, in line with the 10 principles of the global strategy and plan of action on public health, innovation and intellectual property (contained in the annex to resolution WHA61.21 (2008)). Guided by the report of the comprehensive evaluation and, where appropriate, taking into account other evidence and involving relevant stakeholders, including public sector entities and all categories of non-State actors in line with FENSA involved in biomedical research and development, the programme review will:

   (a) assess the continued relevance of the aim and objectives and the eight elements of the global strategy and plan of action;
   (b) consider the evaluation of the implementation of the global strategy and plan of action so far and its key barriers;
   (c) review achievements, good practices, success factors, opportunities, gaps, weaknesses, unsuccessful efforts, remaining challenges, and value for money;
   (d) invite, over the course of the evaluation, appropriate input and comment from WIPO, WTO, and UNCTAD and other relevant intergovernmental organizations;
   (e) recommend a way forward, including details of what elements or actions should be added, enhanced or concluded in the next stage of implementation of the global strategy and plan of action on public health, innovation and intellectual property, until 2022;
   (f) submit a final report to the Health Assembly, including the assessment of the global strategy and plan of action and recommendations on the way forward.

2. The final report of the overall programme review of the global strategy and plan of action on public health, innovation and intellectual property, focusing on its achievements, remaining challenges and recommendations on the way forward will be presented to the Seventy-first World Health Assembly in 2018 through the Executive Board at its 142nd session.

Decision EB140(8). 31 January 2017

Methods of work

In accordance with resolution WHA68.18, 18 experts were selected from a roster of names proposed by Member States and WHO regional directors to form a review panel. The experts were selected on the basis of their technical competence, expertise and knowledge of the eight elements of the GSPA-PHI and to ensure gender balance, equal regional representation and representation from developing and developed countries. The WHO GSPA-PHI review secretariat supported the review panel in providing an independent, impartial report to the World Health Assembly, through the Executive Board. Full attention was paid to avoiding conflicts of interest, in accordance with WHO's policy of declarations of interest by experts.

The review panel held closed meetings in March, June and September 2017 in Geneva; at the request of the panel, a fourth, intersessional, closed meeting took place at Chatham House in London in August. At these meetings, the panel assessed the comprehensive evaluation of the GSPA-PHI, considered the relevance of the eight elements of the GSPA-PHI and reviewed achievements, good practices, factors for success, opportunities, gaps, weaknesses, unsuccessful efforts, remaining challenges and value for money. WHO technical staff made several presentations to provide input for the panel's deliberations.

At the first meeting, the panel identified the deliverables and timelines and decided to focus on five areas that would serve as the basis for the programme review: (i) changes to the policy context since adoption of the GSPA-PHI in 2008; (ii) current activities related to research and development (R&D) and access; (iii) assessment of the comprehensive evaluation report; (iv) definition of core priorities and drafting of recommendations; and (v) responsibility for implementation and advocacy. The panel met in subgroups to address the first three issues. At the second closed meeting, in June, the panel decided to separate the second issue into two, the first on activities related to R&D and the second on activities related to access, and to combine the fourth and fifth issues (recommendations and assignment of responsibility for implementation). Teleconferences were organized by the review secretariat for the panel subgroup members to discuss plans, clarify content and establish how best the review secretariat could support drafting.

In order to obtain opinions from Member States and stakeholders, the panel issued an on-line survey with five questions: Which elements and sub-elements do you consider should be added, enhanced or concluded in the next stage of implementation? Are there elements, sub-elements or actions that you would add to the strategy? In the context of the GSPA-PHI, how can R&D for and access to health products be improved? Are there any issues that are not included that you consider relevant to R&D and access to health products? The responses were used by the panel in their deliberations.

The review panel further consulted Member States and stakeholders at two open sessions held after the two-day closed meeting at WHO headquarters in June 2017. The sessions were attended by representatives of Member States, United Nations specialized agencies, public sector entities and all categories of non-State actors according to the framework of engagement with non-State actors. The open sessions began with a presentation of the overall review of the GSPA-PHI programme, and participants were encouraged to provide feedback, especially to suggest ways for moving forward. All the meeting reports, including the presentation at the open session, are published on the website of the GSPA-PHI overall programme review *(1)*. Supported by the GSPA-PHI review secretariat, panel members also interviewed stakeholders in industry, the Medicines Patent Pool, the Organisation for Economic Co-operation and Development, the World Trade Organization and UNCTAD.

Various reports, publications, websites and background documents were consulted for the review. Members of the panel were also provided with documentation of specific relevance for the GSPA-PHI, notably the report and annex of the comprehensive evaluation of implementation of the strategy and plan *(2)* and a consolidated version published in 2011 *(3)*.

The initial drafts from the subgroups were circulated by the panel to obtain comments, and marginal comments and proposed textual emendations were incorporated into new drafts, which were the

basis for further discussion at the closed meetings and resulted in new drafts that were agreed upon by the whole review panel. In the latter stages of the review, recommendations and messages were formulated (through live editing) in language that was acceptable to all the members of the panel.

B. Executive summary

Objectives and background

In resolution WHA68.18, the WHO Director-General was requested to establish a panel of 18 experts to review the global strategy and plan of action on public health, innovation and intellectual property (GSPA-PHI). The purpose of the review was to complement the comprehensive evaluation commissioned by the WHO Secretariat with a more policy-oriented, forward-looking perspective. The terms of reference approved by the Executive Board at its 140th session indicated that the panel should be guided by the evaluation, while taking into account other evidence and the views of relevant stakeholders, to:

(a) assess the continued relevance of the aim, the objectives and the eight elements of the GSPA-PHI;
(b) consider the evaluation of implementation of the GSPA-PHI so far and the main barriers to implementation;
(c) review achievements, good practices, factors for success, opportunities, gaps, weaknesses, unsuccessful efforts, remaining challenges and value for money;
(d) invite, during the evaluation, appropriate input and comments from WIPO, WTO, UNCTAD and other relevant intergovernmental organizations;
(e) recommend a way forward, including elements or actions to be added, enhanced or concluded in the next stage of implementation of the GSPA-PHI, until 2022; and
(f) submit a final report to the Health Assembly, including an assessment of the evaluation of the GSPA-PHI and recommendations for the way forward.

The origins of the GSPA-PHI lie in a World Health Assembly resolution in 2003, which requested the Director-General to establish

> an appropriate time-limited body to … produce an analysis of intellectual property rights, innovation, and public health, including the question of appropriate funding and incentive mechanisms for the creation of new medicines and other products against diseases that disproportionately affect developing countries.

As a result, the Commission on Intellectual Property Rights, Innovation and Public Health was established in 2004 and reported in 2006. Its central recommendation was that

> WHO should develop a global plan of action to secure enhanced and sustainable funding for developing and making accessible products to address diseases that disproportionately affect developing countries.

The World Health Assembly decided in 2006

> to establish ... an intergovernmental working group ... to draw up a global strategy and plan of action in order to provide a medium-term framework based on the recommendations of the Commission; …[it] would aim, inter alia, at securing an enhanced and sustainable basis for needs-driven, essential health research and development relevant to diseases that disproportionately affect developing countries ….

The GSPA-PHI that was developed and then adopted by the World Health Assembly in 2008 was wide-ranging, consisting of eight elements, 25 sub-elements and 108 specific actions. The eight elements are listed in Box 1.

Box 1. Elements of the global strategy and plan of action on public health, innovation and intellectual property

Element 1. Prioritizing research and development needs

The health research and development policies of developed countries should adequately reflect the health needs of developing countries. Gaps in research on types II and III diseases and on the specific research and development needs of developing countries in relation to type I diseases should be identified urgently. Better understanding of the health needs of developing countries and their determinants is essential to ensure sustainable research and development on new and existing products.

Element 2. Promoting research and development

There are many determinants of innovation capacity. Political, economic and social institutions in each country should participate in setting health research policy, taking into consideration their realities and needs. The range of measures to promote, coordinate and finance public and private research in both developed and developing countries into types II and III diseases and into the needs of developing countries in relation to type I diseases should be extended substantially. Greater investment in both developed and developing countries is essential.

Element 3. Building and improving innovative capacity

Effective policies to promote the development of capacity in developing countries for health innovation should be framed, developed and supported. Key areas for investment are capacity for science and technology, local production of pharmaceuticals, clinical trials, regulation, intellectual property and traditional medicine.

Element 4. Transfer of technology

North–South and South–South development cooperation, partnerships and networks should be supported in order to build and improve the transfer of technology for health innovation. Article 7 of the Agreement on Trade-related Aspects of Intellectual Property Rights states that the protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare and to the balance of rights and obligations.

Element 5. Application and management of intellectual property to contribute to innovation and promote public health

One of the aims of international regimes on intellectual property is to provide incentives for the development of new health products. Incentive schemes should be explored and implemented, where appropriate, for research and development, especially on types II and III diseases and on the specific research and development needs of developing countries in respect of type I diseases. Capacity for both innovation and the management and application of intellectual property should be strengthened in developing countries and especially full use of the provisions in the Agreement on Trade-related Aspects of Intellectual Property Rights and instruments related to that Agreement, which provide flexibility in taking measures to protect public health.

Element 6. Improving delivery and access

Support for and strengthening of health systems are vital for the success of the strategy, as are stimulation of competition and the adoption of appropriate pricing and taxation policies for health products. Mechanisms to regulate the safety, quality and efficacy of medicines and other health products, with adherence to good manufacturing practices and effective supply chain management, are critical components of a well-functioning health system.

Element 7. Promoting sustainable financing mechanisms

In recent years, donors have provided substantial additional financing to make health products available in developing countries by new mechanisms. Additional financing has also been secured for research and development relevant for the control and treatment of the diseases covered by this strategy. Nonetheless, further, sustainable funding will be essential for long-term research and development for products that meet the health needs of developing countries. The most serious gaps in financing for health products and research and development covered by this strategy should be identified and analysed.

Element 8. Establishing monitoring and reporting systems

Systems should be established to monitor the performance and progress of this strategy. A progress report will be submitted to the Health Assembly through the Executive Board every two years. A comprehensive evaluation of the strategy will be undertaken after four years.

In order to implement the GSPA-PHI, WHO initiated a "quick start" programme, building on existing activities in WHO, and responded to a specific action in the GSPA-PHI to establish an expert working group to examine the financing and coordination of research and development (R&D) and proposals for "new and innovative" sources of funding for R&D. As the report of the expert working group in 2010 failed to satisfy the demands of Member States, a consultative expert working group (CEWG) was established in 2011, which reported in 2012. The CEWG recommended a number of initiatives to improve R&D, including the establishment of pooled funds, prizes, patent pools and open approaches for R&D, such as open-source or open-access publishing. It also recommended that countries commit 0.01% of their gross domestic product (GDP) to government-funded R&D and that a global observatory on health R&D be established to collect data on R&D and financing in order to inform health research investment decisions and improve coordination. It stated that "the time has now come for WHO Member States to begin a process leading to the negotiation of a binding agreement on R&D relevant to the health needs of developing countries".

While Member States have thus far not pursued many of the CEWG recommendations, they did endorse the establishment of a Global Observatory on Health Research and Development and a number of demonstration projects for the development of new health products for which a need had been identified but which remained unaddressed. Recently, a decision was taken to establish the Expert Committee on Health Research and Development, also recommended by the CEWG. WHO has also proposed a pooled fund along lines suggested by the CEWG. However, the funding required for the demonstration projects has not materialized; and the pooled fund has yet to attract funding.

The terms of reference of the GSPA-PHI review adopted at the 140th session of the WHO Executive Board include a request for a report on the overall review to be presented at the Seventy-first World Health Assembly through the Executive Board at its 142nd session. The review panel decided to present the report in five chapters, addressing: the changing context of innovation and access, current R&D in the context of the GSPA-PHI, improving access to health products in the context of the GSPA-PHI, an assessment of the evaluation of the GSPA-PHI, and the way forward.

The changing context of innovation and access (Chapter 2)

The panel reviewed changes in global trends and policies since the GSPA-PHI was adopted in 2008 that might shape its thinking on the future of the GSPA-PHI and reflected on how best it could serve to respond to emerging public health needs and priorities in developing countries. It noted the importance for the review of the Sustainable Development Goals (SDGs), which have replaced the Millennium Development Goals (MDGs). The SDG goal for health (Ensure healthy lives and promote well-being for all at all ages) is more comprehensive than that of the MDGs. It retains disease-specific targets, as did the MDGs, but adds targets for noncommunicable diseases and environmental causes of ill health, strengthening financing and building human resource capacity.

Many parts of the SDG agenda are relevant to the GSPA-PHI. Target 3b is to support R&D and access. Target 3.8 reflects the growing impetus to achieve universal health coverage, including "access to safe, effective, quality and affordable essential medicines and vaccines for all", which corresponds to element 6 of the GSPA-PHI. The SDG agenda is also grounded in the Universal Declaration of Human Rights and international human rights treaties, as reflected in its catch phrase "Leave no one behind". For the GSPA-PHI, an important issue is the balance noted in Article 27 of the Universal Declaration on Human Rights between the right "to share in scientific advancement and its benefits" and the right "to the protection of the moral and material interests resulting from any scientific, literary or artistic production."

The panel also reviewed the relevance to the GSPA-PHI of the findings and conclusions of three recent reports on innovation and access: the *Lancet* Commission on Investing in Health (2013), the *Lancet* Commission on Essential Medicines Policies and the report of the United Nations Secretary-General's High-level Panel on Access to Medicines (2016).

The world has been undergoing an epidemiological transition since 2008, driven by economic development, ageing, increased urbanization, environmental degradation and climate change. While health outcomes have continued to improve overall, the incidences of some diseases, such as diabetes, and of risk factors, such as obesity, have increased dramatically. Diabetes alone is responsible for 1.5 million deaths annually. According to the most recent estimate, noncommunicable diseases kill 40 million people each year, accounting for 70% of all deaths globally and over 80% of premature deaths in developing countries.

Two further threats have become prominent since 2008. One is the threat from disease outbreaks, exemplified by the Ebola viral disease, and other health emergencies, such as those arising from natural disasters and conflict, for which there is inadequate access to health products for prevention and treatment. In response, WHO has developed an R&D blueprint for action to prevent epidemics. The other threat is that posed by antimicrobial resistance (AMR), which jeopardizes both the treatment of diseases, such as gonorrhoea and tuberculosis, for which resistance to current medicines is widespread, and also potentially many types of surgery and chemotherapy. WHO Member States have agreed on an action plan to tackle AMR, and a political declaration has been made by the United Nations General Assembly.

Chapter 2 also addresses developments in intellectual property (IP) management, including the use of the flexibilities within the Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS Agreement); the issue of criteria for patentability, including the experience of India in its revision of its Patent Act in 2005; developments in the use of compulsory licensing and the inclusion of provisions in trade agreements that go beyond TRIPS. The review panel noted some positive developments that respond to various elements of the GSPA-PHI, such as the Medicines Patent Pool and increased availability of patent information on medicines. In most areas, however, there has been little or no progress.

In respect of innovation, some remarkable new technologies have been developed, such as CRISPR-Cas9 and products to treat, for example, HIV and hepatitis C infections. Yet, the pharmaceutical industry has significant difficulty in developing new technologies and, on average, much higher costs for each new medicine approved. In spite of some successes, the number of new products for diseases that affect mainly developing countries still represents a small proportion of all new products coming on the market. Furthermore, funding for R&D on these diseases has not increased sustainably: in 2015, total funding (except for the Ebola virus and related diseases) was at its lowest since 2007.

Some success has been achieved in improving access to health products, including for HIV infection, bed nets to prevent malaria and a new vaccine for meningococcal A meningitis. While there is a dearth of reliable statistics both nationally and globally, access to medicines and health products clearly remains a critical problem. In most developing countries, about 70% of medicines are paid for by patients themselves rather than governments or health insurers, resulting in inequity and inconsistent access, especially to medicines for treating chronic conditions. Since 2008, there has been concern in both developed and developing countries about the price of new patented medicines and, in some cases, also of medicines whose patents have expired. New cancer medicines and combinations highlight these concerns. While there are many new medicines to treat cancer, most cost over US$ 100 000 per treatment, and treatments for some rare diseases cost US$ 500 000 per year. Similarly, the prices of new directly acting agents against hepatitis C virus, which are very effective, strain the healthcare budgets of developed countries and are unaffordable for many in developing countries.

These challenges should be considered in making recommendations on the way forward for the GSPA-PHI. As a result of the implementation of the TRIPS Agreement, it is no longer possible to replicate exactly the experience with antiretrovirals for HIV infection, when competition from generic medicines forced the prices of antiretroviral agents down to very low levels, while innovation continued apace. The challenge is to find other mechanisms that will achieve similar

transformations in relation to medicines to treat other infectious and also noncommunicable diseases.

Current research and development in the context of the GSPA-PHI (Chapter 3)

One difficulty in assessing progress in R&D is the lack of data on diseases that mainly affect developing countries. The main source of information on funding is the G-Finder survey, which has good data from developed countries and philanthropic funders but very little from most developing countries.

While the pipeline for antiretroviral medicines for HIV infection remains robust, the number of products being developed for types II and III diseases (see Box 2) represents a small proportion of all products in development. While 6900 products were estimated to be in clinical development in 2016, G-Finder identified only 485 (7%) for types II and III diseases in 2015. Global investment in R&D for neglected diseases was estimated by G-Finder to have reached US$ 3.67 billion in 2015, of which US$ 631 million were invested in R&D for viral haemorrhagic fevers, a category introduced in 2014 in response to the outbreak of Ebola virus disease. If this spending is excluded, only US$ 3.0 billion were invested in 2015, and spending in that year was actually lower than that in 2008. At the same time, countries have not moved towards the CEWG goal of spending 0.01% of their GDP for financing R&D on types II and III diseases. The most recent G-Finder report indicates that the USA came closest, with 0.007% of GDP, followed by Ireland and the United Kingdom at around 0.0036%, which is significantly lower than what was reported in 2010.

Box 2. Types I, II and III diseases

The classification of diseases into types I, II and III originated in a report from the Commission on Macroeconomics and Health, chaired by Professor Jeffrey Sachs, in 2001. The classification was adopted by the Commission on Intellectual Property Rights, Innovation and Public Health and introduced into the negotiations on the GSPA-PHI.

Type I diseases are defined as those that are incident in both rich and poor countries, with large numbers of vulnerable populations. Type II diseases are those that are incident in both rich and poor countries but with a substantial proportion of cases in poor countries. Type III diseases are those that are overwhelmingly or exclusively incident in developing countries.

Reliance on a few major funders makes overall funding vulnerable to their decisions. In 2015, the United States National Institutes of Health alone accounted for 40% of all funding for R&D on neglected disease and the Bill & Melinda Gates Foundation for a further 17%. Since 2009, reductions in funding by these two organizations have not been counterbalanced by increases in funding from other sources. In 2015, public sector funders supplied close to two thirds of funding, the philanthropic sector a further 21% and industry 15%. Funding for the product development partnerships (PDPs) monitored by G-Finder decreased from a peak of US$ 657 million in 2008 to US$ 450 million in 2015. In spite of the decreased funding, PDPs have had some success, and, according to the most recent estimate, over three fourths of the products in the pipeline are being developed in innovative collaborations between public and private sectors, such as PDPs. New PDPs, such as the Global Antibiotic Research and Development Partnership and the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, have emerged to develop new antibiotics and other products required to tackle AMR. The Coalition for Epidemic Preparedness Innovations was formed in response to issues raised by the Ebola virus disease outbreak, to finance and coordinate the development of new vaccines to prevent and contain infectious disease epidemics.

Little progress has been made in improving the prioritization and coordination of R&D funding; however, the Global Observatory is intended to provide analyses of gaps in health R&D that could guide priority-setting. An essential element will be establishment of a WHO expert committee to

provide technical advice on prioritizing health R&D on the basis of the analyses provided by the Global Observatory.

Various new incentive schemes have been developed to address sub-element 5.3 of the GSPA-PHI on intellectual property. One example is the Global Health Investment Fund, which provides financing for the late-stage development of drugs, vaccines, diagnostics and other interventions against diseases that disproportionately affect developing countries. The Longitude Prize is a £ 10 million prize fund for the organization that develops a cheap, accurate, rapid, easy-to-use test kit for bacterial infections at points of care. Open-source research has been promoted through initiatives such as the Malaria Box (sponsored by the Medicines for Malaria Venture [MMV]), which made available 400 promising patented and non-patented compounds, including from company libraries, for further research by anyone, provided that any results were published in open-access journals.

Element 3 of the GSPA-PHI addresses building innovative capacity, including for conducting clinical trials. To reduce the wide disparity in health research capacity between developed and most developing countries, most of the main funders of R&D into neglected diseases include capacity-building activities, and some private companies have such programmes.

Improving access to health products in the context of the GSPA-PHI (Chapter 4)

The objective of element 6 of the GSPA-PHI is to improve the delivery of and access to health products. As noted above, there are no comprehensive data on access to medicines and other health products in developing countries, although this remains a critical problem. Improved access requires a comprehensive health-systems approach to address all stages of the value chain of medicines and other health products, including needs-based R&D and innovation; effective regulation, manufacturing processes and systems to ensure high-quality products; public health-oriented IP and trade policies; effective selection, pricing and reimbursement policies; integrity and efficiency in procurement and supply; and appropriate prescribing and use. Access also depends on the degree to which countries use prepayment, pooling of resources and sharing of financial risk, rather than out-of-pocket payments, to fund health services, although this topic is not addressed in the GSPA-PHI.

The production of affordable, high-quality medicines and other health products is essential for achieving access goals in both developed and developing countries. The challenges in developing countries may include a lack of the necessary technology, weak physical infrastructure, a scarcity of appropriately trained technical staff and insufficient capacity to ensure adequate regulatory and governance functions. Various initiatives are under way by WHO, UNCTAD, UNIDO and other agencies to strengthen capacity and coordinate support for the manufacture of health products in developing countries, but more should be done.

In the area of IP, the flexibilities of the TRIPS Agreement should be properly incorporated into local legislation. In 2015, the TRIPS Council at the WTO extended the date on which least developed countries can choose to protect pharmaceutical patents and data from clinical trials from 2016 to 2033. WHO has promoted trilateral collaboration with WTO and WIPO for training, capacity-building, symposia and workshops on the topics identified in element 5 of the GSPA-PHI. One product of this collaboration was a joint study in 2013 on promoting access to medical technologies and innovation, designed to provide information for technical cooperation among the three organizations and for policy discussions.

The quality, safety and efficacy of medicines and health products is ensured by strengthening national regulations and the capacity of regulatory authorities, and by promoting good practices at national and regional levels. The WHO Prequalification of Medicines Programme has played an important role by assuring the quality of generic medicines procured with funding from international agencies such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) and was instrumental in making AIDS medicines available and more affordable.

Robust regulatory approval processes are necessary to ensure access to high-quality medicines and medical products. While some developing countries have significant technical and institutional capacity in these areas, many lack both the expertise and the resources for effective regulation. While the strengthening of regulatory authorities is being pursued in these countries, a transitional measure might be to grant marketing approval on the basis of previous decisions by "stringent regulatory authorities" (national drug regulatory authorities that are members, observers or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use according to the Global Fund quality assurance policy) or of approval within the WHO Prequalification of Medicines Programme. Regulation could also be improved by pooling resources within regional harmonization initiatives. The African Medicines Regulatory Harmonization Programme is one example, as is the intention to establish an African Medicines Agency.

The WHO Essential Medicines List has played an increasingly important role in facilitating access to new products, as it has progressively included newer patented products that are effective but expensive (such as for cancer or hepatitis C), thus accelerating their availability and affordability in developing countries.

The panel reviewed the various strategies available to countries to make health products more affordable through pricing policies and procurement. A fundamental issue is lack of negotiating power, which makes it difficult for developing (particularly middle-income) countries to secure affordable prices. Lack of transparency about the costs of R&D and manufacturing also makes it difficult for purchasers to determine a "fair" price that strikes the right balance between a reasonable return on investment and affordability. One means of addressing pricing is health technology assessment (HTA), which can provide evidence on the relation between health benefits and cost, whether products should be purchased or whether they might be purchased if the price were lowered. HTA has been used successfully in several developed countries but is more difficult to apply in developing countries because it requires both clinical and economic expertise and a legal and institutional framework that may not be available.

Joint or pooled procurement at national, regional and global levels has proved to be an effective means for securing the lowest possible prices and could be extended. Examples include the Pan American Health Organization Revolving Fund, UNICEF and Gavi (The Vaccine Alliance) for vaccines and the Global Fund for medicines and other health products. Procurement strategies are, however, only effective when there are competitive markets for quality-assured health products. Improving availability and affordability also requires effective management of the supply chain. Supply chains in developing countries face enormous challenges, including unreliable transport and transport infrastructure, inadequate storage and distribution facilities and lack of an appropriately trained workforce for supply chain management.

Rational use of medicines remains a critical issue. WHO estimates that more than half of all medicines are prescribed, dispensed or sold inappropriately and that half of all patients fail to take them correctly. This is true of all medicines but is particularly acute in the case of antimicrobial agents, inappropriate use of which is a major factor in accelerating the development of AMR. Various initiatives are under way to promote responsible use of antibiotics, including monitoring antibiotic consumption and use and "stewardship" programmes. Such initiatives should be extended and strengthened, especially in developing countries that lack policies and good practices for appropriate use of health products.

Adequate financing is a prerequisite for improving access to health products. External flows of assistance for health have grown very slowly since 2010, and the increase in the proportion of national budgets for health appears to have reversed since 2010. To achieve the SDG targets, donors and countries will have to give greater priority to health. A recent estimate for 67 developing countries suggests that reaching the SDG targets for health service delivery would require additional expenditure of up to US$ 370 billion annually.

Assessment of the evaluation of the GSPA-PHI (Chapter 5)

The panel was asked to review the evaluation of the GSPA-PHI commissioned by WHO in order to: assess its implementation; identify achievements, gaps and remaining challenges; make recommendations on the way forward and inform the programme review. The evaluation covered the eight elements and 25 sub-elements of the GSPA-PHI and the 108 specific actions defined in the action plan for the period 2008–2015. The sources of information included documents, interviews with key informants, the outcomes of focus group discussions, a survey of Member States and stakeholder groups in the GSPA-PHI, a web-based public survey and 15 country case studies.

The GSPA-PHI review panel concluded that the method used for the evaluation had positive elements (combined qualitative and quantitative methods), as it involved stakeholders and detailed national case studies, and that it was comprehensive, presenting detailed data sources, survey results and recommendations stratified by stakeholder. The panel nevertheless concluded that the evaluation made little use of actual data but rather relied on opinions; that most of its conclusions were presented without supporting data or references; and that the 32 recommendations were ambitious, unquantified and revealed lack of familiarity with the main subject matter of the GSPA-PHI, which may account for the lack of specificity of many of the comments and statements. Moreover, the report contained several factual errors.

The two main conclusions drawn from the review of the evaluation are:

- *Little awareness of the GSPA-PHI*. Stakeholders, particularly organizations that are directly responsible for research and health at national level, showed little awareness of the GSPA-PHI. Thus, not even the first step in implementation has been reached. Awareness appeared to be greater the more closely involved the stakeholder was with WHO.
- *The scale and scope of the GSPA-PHI preclude effective implementation*. Full implementation of the strategy would very difficult in developed, favourable settings and extremely difficult in developing country settings. By covering multiple elements in the pathway from research to practice to policy, the GSPA-PHI is too unwieldy for effective implementation. In order to be effective, it would have to impact the work of research funders, researchers, regulators of medicines and health products, funders of medicines and health products and health care regulators and providers at many levels in each jurisdiction nationally and locally and in all Member States. This proposition is not realistic.

The way forward (Chapter 6)

Although progress has been made in certain aspects of both innovation and access, many of the challenges that motivated formulation of the GSPA-PHI remain, and new challenges have emerged. These include a lack of new health products in areas of need and of sustainable financing, the unaffordability of many new medicines, a lack of essential health products and inappropriate use, ineffective delivery and supply chain infrastructure and the absence of robust regulatory frameworks and trained human resources, mainly but not exclusively in developing countries.

A major question is whether the GSPA-PHI in its current form can effectively meet these many challenges in innovation and access and motivate governments and other stakeholders to take concrete steps to address them. As discussed in Chapter 5, one of the main drawbacks of the GSPA-PHI is its ambitious scale and scope. In addition, the recommendations made are general and expressed in such a way that it would be difficult to assess and measure progress. Moreover, the GSPA-PHI lacks a robust strategy and plan for implementation and an efficient governance mechanism.

The terms of reference of the panel were to "recommend a way forward, including details of what elements or actions should be added, enhanced or concluded in the next stage of implementation... until 2022".

The panel considers that the eight elements of the GSPA-PHI remain broadly valid. The main problem is the lack of impact in its implementation. This suggests that the review could best add value by recommending a strategy that is more focused in scope and scale and includes a set of priority actions for each element to address current needs in R&D and access to medicines. These should be specific and feasible, with indicators and deliverables that can be monitored. A mechanism for effective governance of the GSPA-PHI is also required, as well as relevant capacity and tools for implementation and monitoring. To this end, the panel formulated a set of actions, indicators and deliverables, which, if achieved by 2022, would constitute real progress. A necessary condition for success is adequate, sustainable funding by Member States, including for activities that are the responsibility of WHO.

The panel took the view that the recommendations should be directed to the WHO Secretariat and/or Member States rather than to all the stakeholders addressed by the GSPA-PHI. Although the activities of stakeholders are integral to its success, it is for the Secretariat and Member States to encourage their appropriate involvement; furthermore, there is no mechanism for holding stakeholders directly to account. Member States and stakeholders should be fully involved in early planning of the implementation of the GSPA-PHI. A communications strategy and materials should be produced to raise awareness of the GSPA-PHI.

Summary of proposed refinements for the GSPA-PHI

Refinement	GSPA-PHI	Review Panel proposal
More focused action	108 actions	33 actions
Prioritized action	No prioritization	17 high-priority actions
More specific action	31 overarching, often non-specific indicators, for 108 actions	33 measurable, action- and time-specific indicators
Specific responsibility for implementation	Broad assignment of responsibility for broadly defined actions	Responsibility for specific actions assigned to WHO and Member States
Specific responsibility for specific actions on monitoring	WHO and governments to establish monitoring systems, and report periodically to WHO on gaps and needs	WHO to draft implementation plan for publication in 2018, establish a monitoring mechanism to support implementation and publish reports at least annually. Member States to collect and report information to G-Finder

The panel considered that WHO Member States should review its recommendations. One option would be to incorporate the recommendations of the panel, subject to any amendments, into a resolution to be debated at the World Health Assembly.

The panel made the following recommendations for priority actions between 2017 and 2022. High-priority actions are underlined. The dates proposed for achievement of the actions are indicative and may be amended in the proposed detailed implementation plan.

Recommendations

Prioritize research and development needs

- Member States to establish sustainable financing for the Global Observatory on Health Research and Development and the Expert Committee on Health Research and Development. (*Indicator*: Funding secured by 2019 to cover the projected budget up to 2022.)
- The WHO Secretariat to formulate a methodology for prioritizing research and development needs for types II and III diseases and the specific research and development needs of developing countries for type I diseases for use by the Expert Committee on Health Research and Development and by Member States, to enable them to identify, respectively, both global and national research and development priorities. *(Indicato*r: Methodology for prioritizing research and development needs prepared by 2018.)
- Report by the Expert Committee on Health Research and Development identifying health research and development priorities to address unmet medical needs based on evidence from the Global Observatory on Health Research and Development and on information provided by experts and relevant stakeholders. (*Indicator*: List of prioritized research and development needs for types II and III diseases established by 2019, with a final list including type I diseases established by 2020.)

Promote research and development

- Member States to support the WHO Secretariat in promoting transparency in, and understanding of, the costs of research and development. (*Indicator*: Reports on the costs of research and development for health products prepared in 2019 and 2021.)
- The WHO Secretariat to establish an information-sharing mechanism to promote collaboration and coordination in research and development linked to the Expert Committee on Health Research and Development and the Global Observatory on Health Research and Development. (*Indicator*: Establishment of an information-sharing mechanism to improve collaboration and coordination of resource allocation in accordance with research and development priorities by 2020.)
- Member States to promote programmes for collaboration with (and provision of support to) developing countries to strengthen clinical trial capacity and expert networks regionally and, where relevant, nationally. (*Indicator*: Report on mapping of programmes for strengthening clinical trial capacity and expert networks regionally and nationally by 2021.)
- Member States and the WHO Secretariat to encourage funders of research and development to ensure open access to all resulting publications immediately or, at the most, within six months of publication. (*Indicator*: Report by 2022 on new initiatives by funders of research and development to ensure that the resulting publications in peer-reviewed journals are open access.)

Build and improve research capacity

- The WHO Secretariat and Member States to develop and support collaboration programmes between internationally recognized centres for research and development and relevant institutions in developing countries to enable those countries to enhance their capacity across the research and development pipeline. (*Indicator*: Report on new collaboration programmes developed and supported by 2021.)
- The WHO Secretariat to continue providing support to strengthen the capacity of national and regional regulatory functions and systems, including for improving clinical trial regulatory

review and oversight. (*Indicator*: Report on national and regional initiatives for strengthening clinical trial regulatory capacity in developing countries by 2019 and 2021.)

- The WHO Secretariat, in collaboration with Member States, to construct and promote the use of a database of relevant training programmes and materials for scientists and other experts involved in research and development from the public and private sectors in developing countries. (*Indicator*: Database of relevant training programmes and materials established and populated, and its use promoted by 2021.)
- Member States to promote the availability of training courses of certified quality, including online courses, for personnel involved in research and development. (*Indicator*: Monitoring the availability of certified quality training courses on research and development.)
- Member States, with the support of the WHO Secretariat, to develop strategies and strengthen their capacity for policy formulation, regulation, research methodology and ethics, and resource preservation in traditional medicine in line with the WHO traditional medicine strategy: 2014–2023. (*Indicator*: Report on national and regional programmes for developing strategies and strengthening capacity in research and development for traditional medicine by 2022.)

Promote transfer of technology

- The WHO Secretariat to identify mechanisms to increase health technology transfer in the context of the Technology Facilitation Mechanism established by the Sustainable Development Goals. (*Indicator*: Report on the identification of mechanisms to increase health technology transfer in the context of activities related to the Technology Facilitation Mechanism by 2020.)
- The WHO Secretariat to work with the secretariat of WTO to identify how Article 66(2) of the Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS Agreement) could be implemented more effectively in relation to health technology transfer in countries. (*Indicator*: Report on progress on health technology transfer related to implementation of Article 66(2) of the TRIPS Agreement by 2021.)
- The WHO Secretariat to identify new opportunities for collaboration with other United Nations organizations (e.g. UNIDO, UNCTAD) to promote technology transfer as part of local health technology production programmes in developing countries in line with country needs. (*Indicator*: Inter-organizational report on national technology transfer programmes developed and disseminated by 2022.)

Manage intellectual property to contribute to innovation and public health

- The WHO Secretariat, in collaboration with other international organizations working in intellectual property, to advocate for the development of national legislation to fully reflect the flexibilities provided in the TRIPS Agreement, including those recognized in the Doha Declaration on the TRIPS Agreement and Public Health and in Articles 27, 30 (including the research exception and "Bolar" provision), 31 and 31bis of the TRIPS Agreement. (*Indicator*: Inter-organizational report on national legislation and patenting guidelines that include the flexibilities provided in the TRIPS Agreement prepared by 2021.)
- The WHO Secretariat, in collaboration with partners, to promote the further development of databases of patents and non-confidential licensing agreements for health products and facilitate greater access to such databases. (*Indicator*: Monitor coverage and use of existing and new databases of patent and licence information.)
- Member States and other funders, with WHO Secretariat support, to strengthen the Medicines Patent Pool, which may include support for the expansion of its portfolio to cover other diseases or technologies for which the Medicines Patent Pool model can have the most impact.

(*Indicator*: Number of diseases and/or technologies covered by the Medicines Patent Pool's portfolio and amount of funding committed by new donors by 2020.)

- Member States, when negotiating trade agreements, to take into account the impact on public health of adopting provisions that go beyond the requirements of the TRIPS Agreement. (*Indicator*: Assessment by 2022 of evidence that negotiators of new trade agreements have taken account of the public health impact of the adoption of such agreements*.)*

Improve delivery and access

- The WHO Secretariat to develop and share good practices on evidence-based selection and health technology assessment for health products for national use, and support bilateral and regional collaboration between countries. (*Indicator*: Good practices on evidence-based selection and health technology assessment developed and disseminated by 2019. Report on bilateral and regional collaboration programmes prepared by WHO by 2022.)
- The WHO Secretariat to provide guidance to Member States on promoting and monitoring transparency in medicine prices and on implementation of pricing and reimbursement policies. (*Indicator*: Guidance on promoting and monitoring transparency in medicine prices and on implementation of pricing and reimbursement policies developed and disseminated in countries by 2020.)
- The WHO Secretariat, in cooperation with Member States and other partners, to establish mechanisms to monitor patient out-of-pocket expenditure on health products. (*Indicator*: Monitoring patient out-of-pocket expenditure on health products.)
- The WHO Secretariat to continue to support Member States in strengthening national regulatory capacity, regional harmonization and other collaborative initiatives for improving access to new and existing quality-assured medicines and health products. (*Indicator*: Report on progress of national and regional regulatory capacity-building efforts in developing countries by 2021.)
- Member States and funders to support the WHO Prequalification of Medicines Programme to include newer essential health products, encompassing medicines, vaccines, diagnostics or biologicals. (*Indicator*: Number of newer health products included in the portfolio of the Prequalification of Medicines Programme by 2020 and 2022.)
- The WHO Secretariat to develop best practices and implement capacity-building programmes for more appropriate use of new and existing medicines and health products in national clinical practice. (*Indicator*: Best practices developed and capacity-building programmes implemented in countries by 2021.)
- The WHO Secretariat to promote best practices in countries and regional institutions to improve procurement and supply chain efficiency, including for joint procurement. (*Indicator*: Assessment of national and regional initiatives for promoting good practices to improve procurement and supply chain efficiency by 2022.)
- Member States to identify essential medicines that are at risk of being in short supply and mechanisms to avoid shortages, and disseminate related information accordingly. (*Indicator*: Lists of medicines at risk of being in short supply and information on mechanisms for preventing shortages made available and disseminated by 2020.)

Promote sustainable financing mechanisms

- Member States to commit to dedicating at least 0.01% of their gross domestic product to basic and applied research relevant to the health needs of developing countries. (*Indicator*:

Percentage of gross domestic product dedicated to basic and applied research as reported by G-Finder by 2021.)

- Member States to commit to increasing domestic resource mobilization and supporting the Addis Tax Initiative in order to, inter alia, implement the health-related Sustainable Development Goals. (*Indicator*: Data from Member States on domestic resource mobilization gathered by 2021.)
- Member States to encourage the implementation of schemes that partially or wholly delink product prices from research and development costs, including actions recommended by the Consultative Expert Working Group on Research and Development: Financing and Coordination. (*Indicator*: New schemes to partially or wholly delink product prices from research and development costs developed, approved and implemented by 2022.)
- Member States, with the WHO Secretariat's support, to encourage an increase and diversification of funding for product development partnerships. (*Indicator*: Increased and diversified funding for product development partnerships and progress as reported by G-Finder by 2022.)

Establish a monitoring and accountability mechanism

- The WHO Secretariat to draw up a detailed implementation plan and establish a mechanism to support implementation and monitoring of the global strategy and plan of action. (*Indicator*: Implementation plan published and a mechanism for implementation and monitoring of the global strategy and plan of action established in 2018, and progress reports published at least once a year.)
- Member States to commit to providing information to G-Finder. (*Indicator*: Number of countries that have provided information to G-Finder.)

C. Full report

Chapter 1.

Introduction

1.1 Origin

The origin of the global strategy and plan of action on public health, innovation and intellectual property (GSPA-PHI) is in a resolution passed by the Fifty-sixth World Health Assembly in 2003, at which the Secretariat presented a report on IP, innovation and public health *(3)*. The report noted that:

> ... a significant proportion of the world's population, especially in developing countries, has yet to derive much benefit from innovations that are commonplace elsewhere. The reasons range from weak supply systems to unaffordable prices. The factors that drive innovation are often biased against conditions that disproportionately affect the populations of developing countries. ... Innovation to address conditions primarily affecting poor people is held back by a combination of market failure and underinvestment by the public sector. The process of bringing a new product to the market is both expensive and lengthy. Because of the resource implications and the uncertainties involved, creating an environment conducive to successful innovation is essential.

Drawing on this document, the World Health Assembly adopted a resolution *(4)* that requested the Director-General to establish

> an appropriate time-limited body to collect data and proposals from the different actors involved and produce an analysis of intellectual property rights, innovation, and public health, including the question of appropriate funding and incentive mechanisms for the creation of new medicines and other products against diseases that disproportionately affect developing countries.

In pursuance of this resolution, the Commission on Intellectual Property Rights, Innovation and Public Health was established in early 2004. In its report *(5)*, published in April 2006, the Commission made some 60 detailed recommendations. Its central recommendation was that "WHO should develop a Global Plan of action to secure enhanced and sustainable funding for developing and making accessible products to address diseases that disproportionately affect developing countries."

In response to the Commission's report, the Fifty-ninth World Health Assembly in 2006 agreed *(6)*

> to establish ... an intergovernmental working group ... to draw up a global strategy and plan of action in order to provide a medium-term framework based on the recommendations of the Commission; such strategy and plan of action would aim, inter alia, at securing an enhanced and sustainable basis for needs-driven, essential health research and development relevant to diseases that disproportionately affect developing countries, proposing clear objectives and priorities for research and development, and estimating funding needs in this area.

The Intergovernmental Working Group on Public Health, Innovation and Intellectual Property, which involves over 100 Member States, met three times between December 2006 and May 2008 *(7)*. In May 2008, after protracted negotiations, the Sixty-first World Health Assembly adopted the GSPA-PHI *(8)*.

1.2 The global strategy and plan of action on public health, innovation and intellectual property

The aim of the GSPA-PHI, set out in paragraph 13, is to

> promote new thinking on innovation and access to medicines and, based on the recommendations of the report of the Commission on Intellectual Property Rights, Innovation and Public Health, provide a medium-term framework for securing an enhanced and sustainable basis for needs-driven essential health research and development relevant to diseases that disproportionately affect developing countries, proposing clear objectives and priorities for research and development, and estimating funding needs in this area.

Paragraph 14 summarizes the eight elements of a strategy to promote innovation, build capacity, improve access and mobilize resources (see Box 1 above):

- provide an assessment of the public health needs of developing countries with respect to diseases that disproportionately affect those countries and identify their R&D priorities at national, regional and international levels;
- promote R&D on types II and III diseases and the specific research and development needs of developing countries in relation to type I diseases (see Box 2, above, for definitions);
- build and improve innovative capacity for research and development, particularly in developing countries;
- improve, promote and accelerate transfer of technology between developed and developing countries as well as among developing countries;
- encourage and support the application and management of IP in a manner that maximizes health-related innovation, especially to meet the R&D needs of developing countries, protects public health and promotes access to medicines for all, as well as to explore and implement, where appropriate, possible incentive schemes for R&D;
- improve delivery of and access to all health products and medical devices by effectively overcoming barriers to access;
- secure and enhance sustainable financing for R&D and develop and deliver health products and medical devices to address the health needs of developing countries; and
- develop mechanisms to monitor and evaluate implementation of the GSPA-PHI, including reporting systems.

The document then sets out the principles underlying the strategy (see Annex 1) and the eight elements (see Box 1), 25 sub-elements and 108 specific actions.

1.3 Negotiations

As the GSPA-PHI became so large and wide-ranging, covering almost every issue in innovation and access, it is important to remember why it was established and the main sources of controversy during the sometimes tortuous negotiations. A key issue was how the IP regime affects both innovation and access. The basis of the concern of many nongovernmental organizations and a number of governments, exemplified by earlier controversies over access to patented antiretroviral medicines for HIV infection, was the extent to which IP rights restrict affordable access to life-saving health products. Concerns about innovation and access motivated the establishment of the Commission on Intellectual Property Rights, Innovation and Public Health by WHO Member States, which led ultimately to the GSPA-PHI. In terms of innovation, as expressed by the Commission, among others, IP rights "can do little to stimulate innovation in the absence of a profitable market for the products of innovation, a situation which can clearly apply in the case of products principally for use in developing country markets."

That being the case, it was considered important to determine how internationally agreed IP rules, notably the TRIPS Agreement, could be used to facilitate access. The mechanisms included using the "flexibilities" in the Agreement (Box 3) or the imposition of stricter standards for patentability consistent with the TRIPS Agreement. It was recognized that use of such flexibilities was threatened by bilateral or plurilateral trade agreements that demanded IP provisions that were more stringent than those required by the TRIPS Agreement. Correspondingly, some countries were concerned that attempts to weaken IP rights would undermine not just the business model of pharmaceutical companies but also incentives for innovation, which depend on recovering the costs of R&D from the prices charged for health products.

Box 3. Flexibilities of the TRIPS Agreement

The main flexibilities of the TRIPS Agreement relevant to a robust IP framework that balances incentives for innovation and access include:

- granting patents for technical developments that comply with rigorously applied criteria of novelty, inventive processes and industrial applicability (utility) and not for those that are designed to extend exclusivity for commercial reasons;
- parallel importation on the basis of the principle of international exhaustion of rights;
- use of the Bolar provision,[2] which permits manufacturers of generic medicines to conduct additional trials on a protected product before its patents expire;
- use of the "research or experimentation exception", as is done in most countries for technological progress and for pro-competitive purposes;
- use of compulsory licences and government use for non-commercial purposes (Articles 31 and 31bis of the TRIPS Agreement), granted by the administration of courts, as in e.g. Germany and the USA.
- use of pre- and post-grant opposition to patent applications that are available to any interested party, as allowed in many countries (including the European Patent Office, India and the USA); and
- protection of data from the testing of new chemical entities under the discipline of unfair competition, in accordance with the requirement established by Article 39.3.

A solution to this conundrum, proposed by a number of nongovernmental organizations and countries, was the concept of "delinkage", whereby recovery of R&D costs was delinked from the price of products. In some formulations, delinkage would be done through a treaty. After prolonged negotiations, the GSPA-PHI proposed to

> encourage further exploratory discussions on the utility of possible instruments or mechanisms for essential health and biomedical R&D, including inter alia, an essential health and biomedical research and development treaty (2.3.c)

and to

> explore and, where appropriate, promote a range of incentive schemes for research and development, including addressing, where appropriate, the delinking of the costs of research and development and the price of health products, for example through the award of prizes, with the objective of addressing diseases that disproportionately affect developing countries (5.3.a).

During the negotiations, the relevance of R&D on type 1 diseases (see Box 2, above) for developing countries was a matter of considerable debate. Some countries argued that, because these diseases

[2] In patent law, research and tests for regulatory approval on products such as drugs do not constitute infringement of a patent term. This exemption is known in Canada as the "Bolar" provision, after the case Roche products v. Bolar Pharmaceutical. Article 30 of the TRIPS Agreement states that "Members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties."

are prevalent in developed countries, the financial incentives for R&D were adequate to meet the needs of both developing and developed countries; therefore, the scope of the GSPA-PHI should be confined to types II and III diseases. Others argued that health products designed principally for developed countries, in which the main market demand existed, were not necessarily suited to the particular needs of developing countries. Until the very end of negotiations, some countries asked for further restriction of the types of diseases covered by the GSPA-PHI (e.g. restricting type II diseases to HIV infection and tuberculosis). The outcome was the rather unwieldy, not entirely meaningful compromise formulation that the GSPA-PHI should "promote research and development focusing on type II and type III diseases and the specific research and development needs of developing countries in relation to type I diseases".

Whether or not delinkage is pursued, increasing R&D on diseases that mainly affect developing countries will require funding additional to that from the price paid for the product, in the absence of a profitable market. Thus, one issue in the negotiations was whether a global fund for R&D on diseases that principally affect developing countries should be established. The countries that would be expected to be the main contributors to such a fund vehemently opposed this proposal, and the compromise was one of the "specific actions" in the GSPA-PHI:

> establish a results-oriented and time-limited expert working group under the auspices of WHO and linking up with other relevant groups to examine current financing and coordination of research and development, as well as proposals for new and innovative sources of financing to stimulate research and development related to Type II and Type III diseases and the specific research and development needs of developing countries in relation to Type I diseases (7.1.a).

A further controversial issue was nominating the stakeholders responsible for pursuing specific actions; this was not agreed until the rest of the GSPA-PHI had been adopted by the World Health Assembly in 2008. Much of the controversy revolved around the role of WHO in relation to IP-related matters covered by the GSPA-PHI. Some countries argued that WHO should defer in such areas to WIPO or WTO. Others argued that WHO's mandate included the interactions between IP and public health. In particular, this applied to the stakeholders responsible for discussions about an R&D treaty. In the end, WHO was excluded from the list of stakeholders for this action (2.3.c).

1.4 Outcomes at WHO

The main text of the GSPA-PHI, other than time-frames, progress indicators, the stakeholders for certain actions and funding requirements, was agreed at the Sixty-first World Health Assembly in resolution WHA61.21 *(10)*. The resolution requested the Director-General urgently to finalize the outstanding components of the GSPA-PHI, urgently to establish the working group on financing and coordination referred to in paragraph 7.1.a of the document, and to establish a "quick start" programme to begin implementation of the strategy. The remaining parts of the GSPA-PHI were completed and agreed at the Sixty-second World Health Assembly in 2009, as documented in resolution WHA.62.16 *(11)*. The main elements were:

- *Time-frame*: The time-frame for the majority of specific actions was set as 2008–2015, the end date coinciding with the that of the MDGs.
- *Progress indicators*
- *Stakeholders*: The remaining 10 specific actions were agreed upon. As noted above, WHO was excluded from discussions on a possible treaty (2.3.c) but was included as a lead stakeholder in discussions on incentive schemes, including possible delinking arrangements (5.3.a).
- *Funding requirements*: The WHO Secretariat estimated that the cost of implementing the GSPA-PHI would be US$ 2 064 billion for the period 2008–2015, and the cost of additional R&D was estimated at US$ 147 154 billion, estimated to represent 12% of the total expenditure for biomedical R&D projected for that period *(12)*. Separately, the cost to WHO's budget was

estimated at US$ 350 million, of which 60% could not be accommodated within existing or projected budgets *(11)*.

The "quick start" programme

In 2008, the Secretariat undertook an Organization-wide exercise to identify existing activities that could contribute to implementation of the GSPA-PHI. Additional activities initiated in 2008 under the "quick start" programme fell within the following broad areas: (i) mapping global R&D activities, identifying research gaps and setting research priorities; (ii) supporting R&D and promoting standard-setting for traditional medicines in developing countries; (iii) developing and strengthening regulatory capacity in developing countries; and (iv) developing a monitoring and reporting framework *(13)*.

Expert Working Group on Financing and Coordination of Research and Development

The Expert Working Group on Research and Development Financing, composed of 24 members, was established in November 2008. It met three times in 2009, before delivering a summary of its report to the Executive Board in January 2010 *(14)* and its final report *(15)* to the World Health Assembly in the same year.

At the consultation before the 2010 World Health Assembly, some Member States, mainly developing countries, indicated that the report failed to meet their expectations. Some considered that proposals they had submitted had been rejected without due consideration or explanation. Other concerns included:

- insufficient attention to delinking the costs of R&D from the price of health products;
- inadequate accounting for the relevant aspects of IP rights in the criteria used to evaluate proposals;
- common proposals for innovative financing mechanisms and for financing health and development in general;
- little attention to research into the broader health systems barriers that limit access to care; and
- no proposals to redress limitations in current coordination mechanisms.

Several Member States acknowledged the limitations to current mechanisms for coordinating R&D. While mechanisms exist in relation to specific diseases, a comprehensive overview of activities and resource flows remained elusive. Several Member States suggested that WHO take a more proactive role in this area *(16)*.

At the Health Assembly, most speakers representing developing countries voiced these and other concerns about the report and suggested that a new expert group or an intergovernmental process be established to address them. Member States eventually agreed to a resolution calling for "a consultative expert working group on research and development: financing and coordination" *(17)*.

Consultative Expert Working Group on Research and Development

The Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG), composed of 20 members, reported to the World Health Assembly in 2012 *(18)*. In its report, in line with its terms of reference, the CEWG reviewed various incentive schemes and proposals for innovative sources of financing. It considered that the following proposals best met its criteria:

- a global framework on R&D;
- open approaches to R&D and innovation;
- pooled funds;

- direct grants to companies;
- milestone prizes and end prizes; and
- patent pools.

With regard to new, sustainable sources of funding, the CEWG considered that some form of taxation was the most fruitful avenue to explore. It considered, however, that it would be unrealistic, given the multifaceted nature of development needs, to devote one, specific, new source that would generate significant amounts of money on a global scale to health R&D of relevance to developing countries. Rather, it considered that a portion of any new source of funding that might emerge should be used to improve health as an acknowledged development priority and that another portion should be devoted to currently underfunded areas of R&D, including those within the CEWG mandate. Taxes such as "sin" taxes (e.g. on fat or sugar) should be considered by each country within its context, whereas taxes such as airline taxes (as currently implemented in some countries), a financial transaction tax or a tobacco solidarity contribution could be sources of funding for an international mechanism to supplement national resources.

The CEWG suggested the following targets for national spending on health R&D relevant to the GSPA-PHI mandate:

- All countries should commit themselves to dedicate at least 0.01% of their GDP to government-funded R&D on mandated diseases. (This was the proportion of GDP spent by the USA at that time on R&D for such diseases.)
- Developing countries with potential research capacity should aim to commit 0.05–0.1% of their GDP to government-funded health research of all kinds.
- Developed countries should aim to commit 0.15–0.2% of their GDP to government-funded health research of all kinds.

In respect of coordination, the CEWG considered that WHO should play a stronger central role in improving coordination of R&D on the health needs of developing countries. The main elements of such coordination by WHO should be:

- a global health R&D observatory to collect and analyse data, including financial flows to R&D and the R&D pipeline, and to learn lessons; and
- advisory mechanisms, comprising a network of research institutions and funders, that might provide input to an advisory committee that could be based on the current Advisory Committee on Health Research.

In conclusion, the CEWG considered it time to consider new ways to achieve the objectives with which WHO Member States had been grappling for so long. A coherent global framework was required that combined the different elements and recommendations into a concerted mechanism. It therefore proposed that discussions on negotiation of a R&D convention be initiated. The principles that might underlie such a convention were already agreed in the GSPA-PHI (see Annex 1). It also suggested a number of objectives and elements relating to financing and coordination.

The 2012 World Health Assembly welcomed the analysis in the CEWG report and asked the Director-General to hold an open-ended meeting of Member States that would thoroughly analyse the report and the feasibility of the recommendations and prepare proposals or options for research coordination, financing and monitoring of R&D expenditure *(19)*.

The open-ended meeting in November 2012 did not reach agreement on the CEWG's recommendations for an R&D convention or on taxation, resource-raising or expenditure targets. Instead, it proposed a draft resolution with a number of recommendations to Member States and the WHO Secretariat that were based on, or derived from, some of the recommendations of the CEWG. This was finalized and approved by the World Health Assembly in 2013 *(20)*. The Director-General was requested to:

- establish a global health R&D observatory to collect data in order to identify gaps and opportunities for health R&D;
- facilitate implementation of a few demonstration projects to address identified gaps; and
- convene another open-ended meeting to assess progress in health R&D monitoring, coordination and financing, including further analysis of the report of the CEWG.

1.5 Follow-up to the report of the Consultative Expert Working Group on Research and Development

The CEWG report and its predecessor, the report of the Expert Working Group on Research and Development Financing, were the direct products of one of the few specific actions in the GSPA-PHI (7.1.a) and can be regarded as achievements attributable to the GSPA-PHI. Since 2012, "Follow up of the report of the Consultative Expert Working Group on Research and Development: Financing and coordination" has been a standing item on the agenda of each World Health Assembly. Correspondingly, the recommendations of the CEWG that have been pursued, albeit not always in the way that the CEWG intended, should be regarded as outcomes of the GSPA-PHI.

Global Observatory on Health Research and Development

A demonstration version of the Global Observatory on Health Research and Development was launched in 2016 *(21)*. Although `proposed by the CEWG, it responds fairly directly to sub-element 1.1 of the GSPA-PHI – "mapping global research and development with a view to identifying gaps in research and development on diseases that disproportionately affect developing countries." It integrates information on funding for health R&D, health products in the pipeline, clinical trials and research publications, and its remit and functions will be extended if it receives additional resources. It has been tasked with collecting data on R&D on AMR and epidemic preparedness. The outputs of the Observatory will include an online portal, and analyses of gaps in health R&D based on a review of the data collected, which will contribute to priority-setting as part of the coordination of health R&D.

Health research and development demonstration projects

These projects, called for in resolution WHA 66.2, were intended to demonstrate the R&D principles favoured by the CEWG and also to respond to sub-element 2.2 of the GSPA-PHI – "promoting upstream research and product development in developing countries". After a prolonged process of selection, six projects were identified, including on leishmaniasis, malaria and schistosomiasis. Funding from Member States has, however, amounted to only about US$ 11 million, while the estimated requirement for the demonstration projects and the Observatory was US$ 85 million *(22)*.

The Expert Committee on Health Research and Development

Also in response to the CEWG report, the 2016 World Health Assembly requested the Director-General to establish a WHO expert committee on health R&D to provide technical advice on priorities and areas of potential market failure, on the basis, inter alia, of analyses provided by the Global Observatory *(23)*. The priorities defined by the Expert Committee will be operationalized with the voluntary pooled fund (see below) for health R&D. Its work will include preparing calls for proposals by analysing product profiles and the existing pipeline of products and technologies; evaluating and selecting the projects best suited for funding; and monitoring and reviewing funded projects to measure progress and evaluate their potential impact. The core principles of affordability, effectiveness, efficiency and equity and the principle of delinkage will be applied *(24)*. This Committee will replace the WHO Advisory Committee on Health Research, and members are currently being selected.

A voluntary pooled fund

WHO has proposed a voluntary pooled fund for R&D, with a target disbursement of US$ 100 million annually over 10 years. The fund would cover a diversified portfolio of 35–40 research projects on priorities identified by the Expert Committee on Health Research and Development. Its purpose would be to operationalize some of the principles and recommendations formulated by the CEWG, including the core principles of affordability, effectiveness, efficiency, equity and delinking the costs of investment into R&D from the volume and price of the resulting health products. It would favour open collaboration and sharing of R&D results. Recipients of grants would have to adhere to the principles of transparency and knowledge-sharing. Recipients who brought to the market products developed with funding from the pooled fund would have to commit to an affordable pricing policy and to manage any IP in such a way as to prioritize access. Various mechanisms for conventional and innovative financing proposed by the CEWG are under consideration *(22)*.

Chapter 2.

The changing context of innovation and access

2.1 Introduction

There have been a number of important developments since 2008 in innovation for, and access to, medicines and health products in both developing and developed countries, many of which have implications for our review. In spite of the financial crisis of 2008, economic growth and poverty reduction have been rapid in many developing countries, which has improved health and made more resources available for health care. Yet, overall, countries' health budgets have not risen as fast as general public expenditure, and resources for R&D for diseases that mainly affect developing countries are for the most part no higher now than in 2008.

A notable shift in the policy context is the transition from the MDGs to the SDGs, which has broadened and deepened the efforts of the international community to end poverty and ensure sustainable development. There has also been a continuing shift in the global burden of disease, driven by an ageing world population and rapid urbanization, amidst heightened concern about the world's ability to deal with infectious disease outbreaks and other health emergencies and the threat posed by AMR.

The GSPA-PHI was established to provide a medium-term framework for an enhanced, sustainable basis for health R&D relevant to diseases that disproportionately affect developing countries. An important part of our work is to review developments since 2008, including changes in the policy context. In some respects, innovation in health technology has flowered, with many new products on the market (e.g. for cancer and hepatitis), but there are still few effective treatments (or diagnostics or vaccines) for many diseases that mainly affect developing countries (e.g. tuberculosis and several emerging or neglected diseases). There is also concern about how existing treatments for all types of disease can be made available, accessible and affordable in developing countries. In the area of IP management, there have been some encouraging developments, but many of the difficult and contentious issues in innovation and access remain. The high prices of many health products pose profound difficulty for access in both developing and developed countries. This chapter reviews the main developments since 2008 in order to establish the context for our analysis.

2.2 From the Millennium Development Goals to the Sustainable Development Goals

The 17 SDGs and their 169 targets are broader in scope and go further than the MDGs by addressing the root causes of poverty and the universal need for development that works for all people *(25)*. The goals cover the three dimensions of sustainable development: economic growth, social inclusion and environmental protection. Building on the success and momentum of the MDGs, the new goals cover more ground, in order to address inequalities, economic growth, decent jobs, cities and human settlements, industrialization, oceans, ecosystems, energy, climate change, sustainable consumption and production, peace and justice. Unlike the MDGs, which were directed mainly at developing countries, the SDGs are universal and apply to all countries. A core feature of the SDGs is their strong focus on means of implementation – mobilization of financial resources, capacity-building and technology – as well as data and institutions.

The health goals of the MDGs focused on three areas: child mortality (goal 4), maternal health (goal 5) and major infectious diseases, HIV/AIDS, malaria and tuberculosis (goal 6). Much was achieved, but most of the goals were not met. Child and maternal mortality fell by about half against the respective targets of two thirds and three quarters. The target for the number of new HIV infections annually was largely met, falling by 40%, but the hugely ambitious target of universal access to treatment by 2010 was not. Nevertheless, the increase from very few people on treatment in 2000 to over 15 million in 2015 is impressive. The incidence of malaria decreased by nearly 40% and

mortality by nearly 60%. The incidence and mortality of tuberculosis also decreased but more slowly in the absence of new treatments and vaccines and in the face of growing multi-drug resistance *(26)*.

The SDG agenda is grounded in the Universal Declaration of Human Rights and international human rights treaties, as reflected in its catch phrase "Leave no one behind". It also reflects the WHO Constitution, which states that "The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition". WHO's only objective in Article 1 of the Constitution is "the attainment by all peoples of the highest possible level of health" *(27)*. For the GPSA, a key issue is the balance to be achieved between the two statements in Article 27 of the Universal Declaration on Human Rights *(28)*:

1. Everyone has the right freely to participate in the cultural life of the community, to enjoy the arts and to share in scientific advancement and its benefits.
2. Everyone has the right to the protection of the moral and material interests resulting from any scientific, literary or artistic production of which he is the author.

This article is quoted without comment in the preamble to GPSA-PHI (paragraph 10) but is not mentioned elsewhere. It is also at the root of the "policy incoherence" referred to in the terms of reference of the United Nations High-level Panel on Access to Medicines (see Chapter 2.3).

The SDG health targets are listed in Box 4.

Box 4. Targets of SDG health goal 3: Ensure healthy lives and promote well-being for all at all ages

3.1 By 2030, reduce the global maternal mortality ratio to less than 70 per 100,000 live births.

3.2 By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births.

3.3 By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases.

3.4 By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and wellbeing.

3.5 Strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol.

3.6 By 2020, halve the number of global deaths and injuries from road traffic accidents.

3.7 By 2030, ensure universal access to sexual and reproductive health-care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes.

3.8 Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all.

3.9 By 2030, substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination.

3.a Strengthen the implementation of the World Health Organization Framework Convention on Tobacco Control in all countries, as appropriate.

3.b Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all.

3.c Substantially increase health financing and the recruitment, development, training and retention of the health workforce in developing countries, especially in least developed countries and small island developing States.

3.d Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks.

Many parts of this agenda are relevant to the GSPA-PHI. Of particular relevance, is, of course, target 3.b, which specifically identifies noncommunicable diseases, many of which are types I and II. It is clear, however, that other targets (notably 3.3) will not be achievable in the absence of new health technologies, including vaccines, medicines and diagnostics. Target 3.8 reflects the growing impetus to achieve universal health coverage, including achieving "access to safe, effective, quality and affordable essential medicines and vaccines for all". The health-related SDGs therefore support and legitimize important parts of the GSPA-PHI.

The SDG agenda is more comprehensive than that of the MDGs. It retains disease-specific targets but adds targets for noncommunicable diseases and environmental causes of ill-health and notably the goal of achieving universal health coverage, strengthening financing and building human resource capacity. It therefore shifts the emphasis towards a comprehensive, system-wide approach *(29)*.

2.3 Recent thinking on innovation and access

Since 2008, three other major reports have been published that bear on innovation and access are relevant to the GSPA-PHI.

In 2013, the *Lancet* Commission on Investing in Health published "Global health 2035: a world converging within a generation" *(30)*. Its theme, captured in the title, is that, with rising incomes in the developing world and continued improvements in health and delivery technologies, a goal that is achievable for nearly all countries in 2035 is to reduce the rates of infection and maternal and child mortality to the current levels of the four best-performing middle-income developing countries (Chile, China, Costa Rica and Cuba). It argued that new tools would be essential to achieve this goal and that a "substantial portion" of development assistance should be devoted to R&D. It endorsed a move towards universal health coverage by what it called "progressive universalism". It recommended public financing of a defined set of interventions for all, particularly for the health needs of the poor, at no cost to the patient. It also envisaged a "larger package of interventions", financed by a variety of mechanisms (taxation, insurance, co-payments), to which the poor would also have free access.

The United Nations Secretary General's High-level Panel on Access to Medicines was established to "review and assess proposals and recommend solutions for remedying the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies". Published in 2016, the report *(31)* made a number of recommendations on the use of flexibilities in the TRIPS Agreement, patent databases, the relations between IP, financing and several other policies, which reflect elements of the GSPA-PHI. It did not extensively address issues of the transfer of technology or much of the agenda on delivery and access covered by the GSPA-PHI. While acknowledging the importance of the many other factors that restrict access to health care, it restricted its focus to the nexus between IP and human rights, trade and public health. It raised a number of issues that are not addressed, at least directly, in the GSPA-PHI.

- Countries should make full use of the policy space available in Article 27 of the TRIPS Agreement by adopting and applying rigorous definitions of invention and patentability that curtail the "evergreening" of patents, to ensure that patents are awarded only when they include genuine innovation.
- Governments should adopt and implement legislation to facilitate the issuance of compulsory licences.

- Governments and the private sector should refrain from explicit or implicit threats, tactics or strategies that undermine the right of WTO Members to use flexibilities in the TRIPS Agreement.
- Governments engaged in bilateral and regional trade and investment treaties should ensure that these agreements do not include provisions that interfere with their obligations to fulfil the right to health.
- Universities and research institutions that receive public funding must prioritize public health objectives over financial returns in their patenting and licensing practices.
- Building on current discussions at WHO, the United Nations Secretary-General should initiate a process whereby governments can negotiate global agreements on the coordination, financing and development of health technologies. This includes negotiations for a binding R&D convention that delinks the costs of R&D from end prices to promote access to good health for all. As a preparatory step, governments should form a working group to begin negotiating a code of principles for biomedical R&D.
- Governments should require manufacturers and distributors of health technologies to disclose to drug regulatory and procurement authorities information pertaining to: (i) the costs of R&D, production, marketing and distribution of health technology being procured or given marketing approval, with each expense category separated; and (ii) any public funding received in the development of the health technology, including tax credits, subsidies and grants.

The report was accompanied by the comments of some panel members who considered either that the recommendations did not go far enough or that they went too far. A particular point of contention was whether patented medicines on the WHO Essential Medicines List should be subject to automatic compulsory licensing. The recommendation was rejected by a sizeable minority of the panel "because of concerns over the potential incompatibility of such measures with the TRIPS Agreement and the unintended consequences that may result from such an approach." The "unintended consequences" refer to the possible chilling effect on investment in R&D by the private sector.

The third report, that of the *Lancet* Commission on Essential Medicines Policies, also published in 2016, identified five core challenges *(32)*.

- Paying for a "basket" of essential medicines: Recommendations include adequate financing including additional external support for developing countries and reducing the amount of out-of-pocket spending on medicines.
- Making essential medicines affordable: Recommendations include better monitoring of prices and availability and a comprehensive set of policies to make both patented and generic medicines more affordable, use of health technology assessments (HTAs) and greater transparency in sharing information on health and medicines.
- Assuring the quality and safety of medicines: Recommendations include promoting harmonization of quality assurance through a standard, international regulatory dossier and reducing duplication by national regulators; changing the WHO Prequalification of Medicines Programme's remit to cover newer essential medicines and biosimilar products, better procurement practices and more independent assessments of the performance of national regulatory bodies.
- Promoting good-quality use of essential medicines: Recommendations include establishing independent pharmaceutical analytical units to promote good-quality use and involving stakeholders in identifying problems in appropriate use of medicines and in ways to modify behaviour that leads to inappropriate use.
- Developing essential medicines that are lacking: Recommendations include identifying a list of essential medicines that are lacking through the WHO Global Observatory on Health Research and Development, a global R&D policy framework with financing and delinking mechanisms, a patent pool for all essential medicines and better alignment of pharmaceutical research

priorities with global health needs, including investment of a percentage of profits in products that are necessary but not commercially attractive.

2.4 Epidemiological change

The world has been undergoing an epidemiological transition since 2008. While economic development has improved health outcomes overall, the burden of communicable diseases is decreasing and life expectancy is rising, the prevalence of some diseases (such as diabetes *(33)*) and risk factors (such as obesity *(34)*) has increased dramatically. The burden of communicable diseases decreased between 1990 and 2015, particularly those of malaria and HIV/AIDS, and exposure to poor sanitation and indoor air pollution and childhood undernutrition have dropped, resulting in dramatic decreases in the burdens of diarrhoea and pneumonia in children. As populations grow and the average age increases, however, the total burden of disability is rising rapidly. Exposure to risk factors linked to development, including obesity, high blood sugar, air pollution and drug use, has increased markedly between 1990 and 2015, making these factors among the most pressing targets for intervention *(35)*.

The epidemiological transition has been driven by economic development, ageing, increased urbanization, environmental degradation and climate change. According to the most recent estimate, noncommunicable diseases kill 40 million people each year, equivalent to 70% of all deaths globally. Diabetes alone is responsible for 1.5 million deaths annually *(33)*. Over 80% of deaths from noncommunicable diseases occur in low- and middle-income countries *(36)*, where they are fast replacing infectious diseases and malnutrition as the leading causes of disability and premature death. Tobacco use (including exposure to second-hand smoke) accounts for 7.2 million deaths every year, while excess salt or sodium intake accounts for 4.1 million deaths annually *(37)*.

Since 2008, improving outbreak response has received greater attention, as a result of outbreaks such as those of H1N1 virus, Middle East respiratory syndrome, Zika virus disease and, notably, Ebola virus disease. Such outbreaks must be contained at an early stage to avoid potentially massive epidemiological consequences. Population growth, urbanization, increased national and international mobility and closer contact with wildlife have increased people's vulnerability. These epidemics disproportionately affect developing countries, where the health systems are often too weak to respond. Similarly, while life expectancy has increased in most countries, certain countries experienced decreases between 2005 and 2015, largely because of war and conflict. For example, life expectancy in the Syrian Arab Republic has fallen by 7.3 years for women and by 11.3 years for men. Libya experienced a smaller reduction. Overall, the number of deaths during conflict rose between 2005 and 2015 by over 400% to 170 000 *(38)*.

AMR has also come to the fore since 2008, and the GSPA-PHI does not address it. AMR is a major threat to the treatment of many common diseases: if the situation deteriorates further as resistance continues to grow, the consequences for modern medicine and therefore morbidity and mortality could be extremely serious. Globally, multi-drug-resistant tuberculosis develops in nearly 500 000 people each year. Gonorrhoea is on the verge of being untreatable as a result of resistance to all the first-line and most of the second-line treatments. In the worst case, AMR could threaten the safety of many surgical operations and cancer chemotherapy *(39)*.

This review of epidemiological change suggests that the GPSA-PHI should place more emphasis on addressing noncommunicable diseases and should include elements to address outbreaks, environmental challenges and AMR.

2.5 Developments in intellectual property

The GSPA-PHI is designed to support countries in using the flexibilities in the TRIPS Agreement (see Box 3, above), as recognized in the 2001 Doha ministerial declaration on the TRIPS Agreement and public health *(40)*. The issues covered include compulsory licensing in countries without

manufacturing capacity, taking into account the implications for public health of IP protection that is more extensive than that of TRIPS, accessing patent databases and exploring new incentive schemes for R&D, including delinking the costs of R&D and the price of health products. The GSPA-PHI acknowledges the importance of sustaining access to existing medicines in least-developed countries.

Some positive developments have occurred, such as the establishment of the Medicines Patent Pool and greater availability of patent information on medicines, but in most areas there has been little or no progress. This chapter highlights other developments since 2008 that are relevant to our review.

The GSPA-PHI does not address standards of patentability directly. This subject is important for preventing the patenting of trivial innovations and curbing the practice of "evergreening", which can be used to extend the market exclusivity of patented products for commercial purposes *(41)*. Some, particularly in industry, argue that this practice may discriminate against "incremental innovations" that are of benefit to public health *(42)*.

Certain countries have recently adopted laws that provide for more rigorous standards of patentability. South Africa's recent draft IP policy envisages examination of patents for high-priority sectors (including pharmaceuticals) and patentability criteria "consistent with the State's constitutional obligations, developmental goals, and public policy priorities" *(43)*. Other countries, such as Argentina, have adopted more rigorous guidelines for patent examination *(44)*. Many countries, however, apply flexible patentability standards that allow the granting of "secondary" patents that may be used strategically to delay or prevent legitimate competition from manufacturers of generic products.

Much attention has been paid to developments in India because of the country's importance as a supplier of generic health products to developing counties. For example, in 2015, Indian companies supplied over 80% of antiretroviral medicines to the developing world *(45)* and 60% of the vaccines purchased by Gavi in 2014 *(46)*. Patenting of a product in India prevents manufacture of generic products by Indian companies, who could otherwise sell the generic version of a product to third countries without an enforceable patent or under compulsory licence. Section 3(d) of the Indian Patent Act, as amended in 2005 when India was obliged to comply with the TRIPS Agreement, states that the following is not an invention

> the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

A landmark case in India was that concerning imatinib (Gleevec), produced by the pharmaceutical company Novartis for the treatment of chronic myeloid leukaemia, one of the most common blood cancers. In 2006, the Indian Patent Office refused Gleevec's patent on the grounds of lack of novelty and an inventive step, because earlier patents had already claimed "all pharmaceutical salt forms of imatinib", and that, under Section 3(d), the new product did not demonstrate enhanced efficacy despite a 30% increase in bioavailability over that of the previous product. After nearly a decade of legal hearings on its patentability, the Supreme Court of India made a final decision in 2013, rejecting Novartis' appeal against the Patent Office's refusal of the patent. The Supreme Court stated that, even if the bioavailability of the drug was improved, it did not demonstrate enhanced efficacy and was not patentable. The Supreme Court noted, however, that their decision did not mean that Section 3(d) bars patent protection for all incremental inventions of chemical and pharmaceutical substances. It was therefore not intended to undo the fundamental change in the 2005 Act, as a result of the TRIPS Agreement, which ended the ban in the 1970 Patent Act on patenting pharmaceutical products *(47)*.

In another case, in 2015, the Indian Patent Office rejected Gilead's patent application for sofosbuvir (Sovaldi), a treatment for hepatitis C, on the grounds that it was not a significant improvement in

terms of therapeutic efficacy over an earlier compound *(48)*. This decision was reversed in 2016, when the Patent Office decided that, in fact, the compound was novel and inventive. Activist groups claimed that the reversal was a result of political pressure from the company and the United States Government *(49)*, and the decision is currently being appealed. Patents on sofosbuvir have also been rejected in Brazil, China and Ukraine.

While some countries have used the flexibilities in the TRIPS Agreement, they are often absent from national laws or were adopted with some limitations, such as a narrow scope for the research exception, geographically limited parallel importation or burdensome procedures for granting compulsory licences. Some governments seeking access to patented medicines and health products have relied on compulsory licences, a mechanism used to grant a third party the right to produce or import a patented product without the consent of the patent owner. Paragraph 5 of the Doha declaration *(40)* confirms that countries have the freedom to determine the grounds for compulsory licences and to determine what constitutes a national emergency or other circumstance of extreme urgency and that their use is not limited to emergencies. A survey in 2012 showed that most compulsory licences were granted between 2003 and 2005 and the number decreased substantially after 2006 *(50)*. The same survey found that, of the 24 compulsory licences counted, 16 were for drugs for HIV/AIDS, four for drugs for other communicable diseases and four for drugs for noncommunicable diseases such as cancer. More than half the compulsory licences were issued in upper–middle-income countries (including Brazil and Thailand). Developed countries have also used compulsory licences, including Canada (to supply medicines to Rwanda in 2007), Italy and the USA *(51)*.

The GSPA-PHI makes one reference to trade agreements, in proposing that the flexibilities in the TRIPS Agreement be taken into account (5.2c). Separately, it proposes that the impact on public health be taken into account in considering more extensive protection than that required by the TRIPS Agreement (5.2b). Such considerations are often introduced during negotiation of trade agreements involving developed and developing countries, when developing countries are invited to accept provisions that go beyond those stated in the TRIPS Agreement in ways that limit access to health products. This usually takes the form of provisions that allow more grounds for patenting than those required by the TRIPS Agreement or extension of market exclusivity periods in ways that are not required by the Agreement, in both cases limiting the scope for generic competition *(52)*.

Since 2008, several major negotiations have been held between developed and developing countries on major trade agreements. These include the Trans-Pacific Partnership agreement, which was negotiated between 2008 and 2015. Its provisions were wide ranging, as were the controversies about them, but one major source of concern was the extent to which it went beyond the TRIPS Agreement in regard to pharmaceutical products. It included provisions allowing the patenting of second uses of known substances, extending patent terms for delays in patent grants or marketing approval and introducing "patent linkage" and data exclusivity provisions that are not required by the TRIPS Agreement (including an 8-year period for biological medicines) and stricter enforcement rules in favour of rights holders *(53)*. The USA withdrew from the agreement in 2017 before it could be ratified. The other parties to the agreement have reopened negotiations and, significantly, are reported to be considering dropping many of the provisions that go beyond TRIPS.

The demise of the Trans-Pacific Partnership has focused attention on the Regional Comprehensive Economic Partnership, a proposed free trade agreement among the ten member states of the Association of Southeast Asian Nations and the six states the Association has free trade agreements with (Australia, China, India, Japan, New Zealand and the Republic of Korea). A draft report in 2015 *(54)* indicated that "TRIPS-plus" measures, similar in some respects to those of the Trans-Pacific Partnership, were under negotiation. The presence of countries in this group such as China and India, which were not in the Trans-Pacific Partnership negotiations, suggests that the outcome may be different from that of the Partnership. The European Union and India have been negotiating a free trade agreement since 2007; one of the issues at stake is the European Union's demands on IP rights *(55)*.

2.6 Developments in innovation

Since 2008, there have been striking advances in technologies relevant for health innovation. For example, developments in synthetic biology, such as the gene editing tool CRISPR–Cas9, offer great promise for accelerating the development of new treatments *(56)*. CRISPR-Cas9 facilitates the production of chimeric antigen receptor T cells for cancer treatment, a technology first approved by the United States Food and Drug Administration in August 2017 *(57)*. Three-dimensional printing is beginning to change the way that drugs are not only manufactured but also administered *(58)*. Precision medicine could potentially result in the development of new targeted therapies and the re-purposing of existing drugs *(59)*; and nanotechnology is already being used to reformulate cancer drugs that failed in human clinical trials because of their toxicity or other issues *(60)*.

However, the industry still faces significant technical difficulties in developing new technologies. For example, the number of new drugs approved per billion United States dollars spent on R&D has halved roughly every nine years since 1950, falling around 80-fold in inflation-adjusted terms *(61)*. Not all the promised benefits of targeted drug discovery and genomics have been delivered *(62)*. One response has been a massive number of mergers and acquisitions as companies strive to rationalize, cut costs and improve R&D productivity. Since 1995, 60 large pharmaceutical companies have been reduced to just 10 *(63)*. The results of studies on whether consolidation has been effective in improving productivity vary *(64)*. What is clear is that smaller biotechnology companies now produce approximately two thirds of the new molecular entities approved by the United States Food and Drug Administration and 70% of the drugs currently in the pipeline *(65)*. Thus, larger companies often boost their R&D pipeline by acquiring the developers of promising technologies. This, for example, is what Gilead did in acquiring Pharmasett, the developers of sofosbuvir, for US$ 11 billion in 2011 *(66)* and in acquiring Kite Pharma, the developer of chimeric antigen receptor T cell technology, for US$ 12 billion in 2017 *(67)*.

Public policy in some countries and market failures have contributed to the commercialization by pharmaceutical companies of more specific therapies to treat fewer patients at ever-rising cost. Companies increasingly focus on higher-priced medicines with smaller markets, in oncology and for other chronic conditions *(68)*. In 2006, the highest selling drug in the USA was Lipitor, a statin, with sales of US$ 8.2 billion at an annual cost to the patient of about US$ 1300 *(69)*. In 2016, the highest selling drug was Humira, an injectable drug for various inflammatory conditions, with sales of US$ 16.1 billion *(70)* and a cost per injection of over US$ 2000. In spite of this tendency, the pipeline for new and improved therapy for HIV infection, for example, remains robust, driven particularly by market prospects in the developed world *(71)*.

The same does not apply to most research on types II and III diseases. Of the 6900 medical products currently in clinical development *(68)*, only 485 (7%) were estimated in 2015 to target types II and III diseases *(72)*. Cancer is by far the most targeted therapeutic area, accounting for almost one third of medicines in development in 2016, followed by prophylactic vaccines, anti-infective agents and anti-diabetics.

The current situation of funding of R&D for diseases that mainly affect developing countries is not reassuring. According to successive reports by G-Finder, global investment in R&D for neglected diseases reached US$ 3.67 billion in 2015, of which US$ 631 million were for viral haemorrhagic fevers, a category introduced in 2014 to capture financing in response to the Ebola virus disease outbreak. When this spending is excluded, only US$ 3 billion were invested in 2015; spending was actually lower than that in 2008 and more than US$ 300 million lower than its peak in 2009. Public sector funding (at US$ 1.925 billion) was also at its lowest since 2007, due mainly to a decrease in funding from the United States Government to US$ 1.387 billion, the lowest recorded since the first G-Finder survey in 2007. The only positive trend was investment by private industry of US$ 471 million, up from US$ 214 million in 2007 *(73)*.

2.7 Access to medicines

Since 2008, there have been some positive developments in access to medicines and other health care products. Notably, 19.5 million people were receiving antiretroviral therapy for HIV infection in 2016 as compared with 4 million in 2008 *(74,75)*. The number of households in Africa with access to at least one insecticide-treated bednet increased from about 30% in 2008 to nearly 80% in 2015 *(76)*. A new vaccine for meningococcal A meningitis was developed to address epidemics of the disease that periodically affected 26 African countries. It was first made available with the support of Gavi in 2010, and by 2016 more than 270 million people had received the vaccine in mass campaigns in those countries *(77)*.

While there has been success in addressing particular diseases, access to medicines more generally remains a problem. Globally, one fourth of health budgets is spent on medicines, the largest item after staffing costs. Moreover, in most developing countries, about 70% of medicines are paid for by patients themselves rather than governments or health insurers. The *Lancet* Commission on Essential Medicines Policies estimated that financing a basic package of 201 essential medicines in all developing countries would cost US$ 77–152 billion (or US$ 13–25 per capita). Public expenditure per capita on pharmaceuticals was estimated to be about US$ 10 per capita in all developing countries and much lower (US$ 2) in low-income countries. Per capita expenditure on pharmaceuticals was US$ 9 in total, including private expenditure. In lower–middle-income countries, total expenditure per capita amounted to US$ 37, of which US$ 25 were borne by patients themselves *(32)*. The SDG health targets are important in that they recognize that these weaknesses should be addressed by promoting universal health coverage, access to high-quality essential health care services and medicines, financial protection and building the human capacity of health systems.

While there is clearly a problem in accessing medicines globally, there are no definitive data on how many people lack access to what medicines. The MDG target – "In cooperation with pharmaceutical companies, provide access to affordable essential drugs in developing countries" – was never monitored and was often ignored in reports on progress towards the MDGs *(78)*. The best data on the prices (and availability) of medicines were derived from surveys within the WHO and Health Action International project on medicine prices and availability *(79)*; however, only 38 of the 194 countries included in the World Health Statistics report in 2015 had gathered survey results between 2007 and 2013 *(80)*. The final report of the MDG task force *(81)* noted that no national data series had been collected systematically in developing countries or aggregated into global figures. The surveys produced ambiguous results, from which no trends could be derived, and "provide(d) more than anecdotal but less than systematic or comprehensive information". Nevertheless they "supported concerns expressed in the Task Force reports about the limited degree of access to affordable essential medicines in low- and middle-income countries."

Concerns that have arisen since 2008 are related to the price of new patented medicines and, in some cases, also medicines on which patents have expired. This is a concern in both developed and developing countries. New cancer drugs and combinations exemplify these concerns. While there are many new medicines to treat cancer, most cost over US$ 100 000 per treatment, and one combination is priced at US$ 252 000. This raises serious questions about the financial sustainability of cancer treatments, as cancer rates rise in ageing populations. Correspondingly, it raises questions about the sustainability of a business model that results in such high prices, which do not always reflect the health benefits procured *(82)*. Similar considerations apply to the introduction of directly acting antiviral agents to treat hepatitis C. These are transformative drugs, which offer the promise of a cure for hepatitis C, in many cases after a 12-week course; previous treatments, which were less successful, involved courses of up to 48 weeks. A course of one drug, sofosbuvir, which was introduced in the USA in 2014, initially cost US$ 84 000. As a result of licensing agreements, discounting and competition, some countries now have access at much lower prices. In a recent analysis of 26 countries within the Organisation for Economic Co-operation and Development and Brazil, Egypt, India and Mongolia, the price of sofosbuvir ranged from US$ 539 per course of treatment in India to US$ 50 000–60 000 in most of the 26 countries (before discounting) *(83)*. The

authors estimated that the total cost of treating all patients with hepatitis C would be equal to at least one tenth of the annual cost of all medicines in the 30 countries studied. In countries where prices are high and the burden of disease is great, the total cost of treating all infected patients would be more than the cost of all other medicines together.

There is a disturbing trend of increasing prices of some drugs that have been off patent for a long time. A notorious case was that of Turing Pharmaceuticals, which, in 2015, increased the price of Daraprim, which it had just acquired from another company, from US$ 13.50 to US$ 750 per pill *(84)*. There are numerous similar examples in which the prices of off-patent dugs, with niche markets, are massively increased. Recently, the United Kingdom Competition and Markets Authority imposed a record fine of £ 84.2 million on the pharmaceutical manufacturer Pfizer and a fine of £ 5.2 million on the distributor, Flynn Pharma, after finding that each broke competition law by charging excessive and unfair prices in the United Kingdom for capsules of phenytoin sodium, an anti-epilepsy drug. This followed price increases of up to 2600% overnight after the drug was deliberately de-branded in September 2012 *(85)*. Phenytoin was first approved for marketing in 1953.

One means of addressing issues of pricing are health technology assessments (HTA), which can provide evidence of the relations between health benefits and costs and a guide to whether products should be purchased, or whether they might be purchasable if the price were lowered. Such arrangements work best when the body that commissions an HTA has sufficient market power to influence the decisions of sellers of products. For example, in the United Kingdom, the National Institute for Health and Care Excellence makes decisions about whether a new technology should be made available under the National Health Service. This gives it considerable influence over the pricing decisions of pharmaceutical companies. For example, in 2015, the Institute rejected the Roche drug Kadcyla for breast cancer because its price at £ 90 000 per treatment was too high in relation to the benefits it offered patients. In 2017, it reversed this decision after reconsidering its original analysis of benefits and because Roche had offered a lower price (the details of which are confidential) *(86)*.

In developing countries, HTAs are more problematic because they require both clinical and economic expertise that may be in short supply, as well as a legal and institutional framework to support them. They may also have fewer possibilities to influence pricing decisions by suppliers of products. Nevertheless, countries such as Thailand have had some success in using HTAs to reduce the price of medicines *(32)*, and other countries are gradually building their capacity in HTA *(87)*.

WHO, with the Netherlands Government, has initiated discussions on the fair pricing of medicines. The exact meaning of “fair pricing” is yet to be defined, but the aim is to discuss options for a fairer pricing system that is sustainable for both health systems and the pharmaceutical industry. This might involve alternative R&D and business models for innovation; facilitating collaboration among payers by extending current networks to include other stakeholders and countries; increasing exchanges of information, for example to assess the value of new products; and promoting transparency in the prices paid, R&D costs, production costs and profit margins. Two forums to discuss these issues were held, in 2016 and 2017 *(88)*.

A key issue is the importance of ensuring the quality, safety and efficacy of medicines and health products. The WHO Prequalification of Medicines Programme, established in 2001, has played an important role by assuring the quality of generic medicines procured with funding from international agencies such as the Global Fund. Its existence led to the establishment of a competitive market for quality-assured generic medicines, initially for treating HIV infection, and it therefore played a key role in the rapid fall in the prices of these medicines after 2001 *(89)*. The programme has since been extended from its initial focus on HIV/AIDS, tuberculosis and malaria to other products, including for reproductive health, neglected tropical diseases, hepatitis and influenza, and biosimilar products for cancer. It also covers vaccines and diagnostics.

The discussion above suggests that implementation of the GSPA-PHI should more directly address means to meet the challenges raised by the products of innovation that potentially offer great

health benefits to patients in developing countries but the prices of which preclude widespread access, even in many developed countries. As a result of the TRIPS Agreement, it is no longer possible to replicate the experience with medicines for HIV infection, when generic competition forced down the prices of antiretroviral agents to very low levels. That was a major factor, with massive international funding for procurement, in bringing about the nearly fivefold increase in the number of people on treatment between 2008 and 2016. The question is whether other mechanisms could help to achieve similar transformations for medicines to treat noncommunicable diseases, particularly cancer but also diabetes and other diseases, as well as infectious diseases such as hepatitis C.

2.8 Conclusion

This review of developments in innovation and access since 2008 suggests a number of orientations that might influence implementation of the GSPA-PHI. In spite of some success in innovation and access, many of the problems that the GSPA-PHI sought to address remain. The funds allocated for R&D on diseases that mainly affect developing countries have not increased, and discussions on finding additional funding since 2008 do not indicate a level of political will needed to change the situation. New developments relevant to innovation and access should be considered.

First, implementation should be based on the SDG agenda, which is broader than that of the MDGs. In particular, the development and accessibility of existing and new health products will be important for achieving the SDG targets and for moving towards universal health coverage. Secondly, the review of epidemiological change above suggests that, in the future, more emphasis should be placed on noncommunicable diseases, which are mainly types I and II diseases, as well as AMR. Thirdly, implementation should take into account continuing issues in IP and sustainable financing. Fourthly, consideration should be given to replicating successes in the treatment of HIV infection in the treatment of other diseases.

Chapter 3.

Current research and development in the context of the global strategy and plan of action

3.1 Introduction

The evolving global disease burden reflects major demographic, socioeconomic and ecological changes, which are shifting demand for new technologies. At the same time, developments in technologies open up opportunities for major advances in public health. For those opportunities to be fully realized with regard to neglected diseases, needs-based innovation is a priority. The development of neglected disease R&D is a core concern of the GSPA-PHI. This chapter addresses the extent to which the imperatives identified in the GSPA-PHI are reflected in current R&D.

Knowing what research is currently being undertaken – where, by whom and supported by which organizations – has been described as a "black hole" in public health *(90)*. Most of the numbers we rely on are contained in the G-Finder survey *(91)*, which has been published annually since 2008, and data provided by a variety of other sources to the Global Observatory on Health Research and Development. G-Finder collects funding data from over 200 private, public and philanthropic organizations on R&D on products for 39 neglected diseases and has recently included data on Ebola virus disease and other viral haemorrhagic fevers. Thus, G-Finder broadly covers health products for types II and III diseases, the area of interest of the GSPA-PHI. In terms of country coverage, however, it tracks R&D funding in only six developing countries: Brazil, Colombia, India, Mexico, South Africa and Thailand *(73)*. What is being done in all other developing countries, including several with significant innovative capacity, falls into the black hole. For a recent study, data on health R&D were found for only 37% of countries, and fewer countries regularly collect relevant statistics *(92)*. Furthermore, the available data are heterogeneous, making it difficult to aggregate and compare them, which is essential for effective monitoring and evaluation. A standard classification system for health R&D is required.

The GSPA-PHI calls for the establishment of monitoring and reporting systems and makes specific reference (8.1.d) to monitoring investments in R&D to address the health needs of developing countries. As already noted, WHO's support in this area includes the Global Observatory for Health Research and Development. Despite such efforts, there is still a long way to go. Better country-level monitoring of health R&D is essential if the Observatory is to fulfil its functions. Designating national health R&D institutes to perform this role would be an important step.

3.2 Prioritization of health research and development

Element 1 of the GSPA-PHI calls for the health R&D policies of developed countries to reflect adequately the health needs of developing countries and sets out three sub-elements and 13 actions to achieve this goal. The problem identified in the GSPA-PHI is that R&D directed at health needs in developing countries is insufficiently incentivized by IP rights, because the commercial prospects of the resulting products are uncertain *(93)*. There has been limited progress in this area. The pipeline for antiretroviral medicines for HIV infection remains robust *(71,94)*; however, beyond that, the number of products for types II and III diseases represents only a small proportion of all products in development. As noted in Chapter 2, 6900 products were estimated to be in clinical development in 2016 *(68)* and only 485 products targeted at types II and III diseases in 2015 *(72)*. Comparable data from an earlier period are difficult to locate, but this finding suggests a significant increase in the number of relevant new health products that are likely to be approved in the coming years. A review in 2013 found that 37 (4%) of the 850 new therapeutic products registered in 2000–2011 were indicated for neglected diseases; of these, 25 products had a new indication or formulation and eight

were vaccines or biological products. It was estimated in 2002 that only 1.1% of new therapeutic products had been developed for neglected diseases in 1975–1999 *(95)*.

More than two thirds (71%) of the US$ 3 billion invested in R&D in 2015 were for the "big three" diseases: HIV/AIDS accounted for US$ 1.01 billion, tuberculosis for US$ 567 million and malaria for US$ 565 million. For other diseases, funding drops sharply. For example, funding for R&D on dengue is less than US$ 100 million, despite growing concern about the spread of the disease, with an estimated 390 million new infections per year *(96)* and 3.9 billion people in 128 countries at risk for infection with dengue viruses *(97)*. Most of the diseases in the G-Finder survey received less than 0.5% of total funding for R&D on neglected diseases, including leprosy, cryptococcal meningitis, trachoma, rheumatic fever, Buruli ulcer and leptospirosis. There are also numerous diseases that occur at incidences too low to be reported in G-Finder, such as nodding syndrome, and almost nothing is known about R&D investment for these diseases.

There are several reasons for the continuing neglect of certain areas, the most obvious being lack of commercial incentive. It has been suggested *(98)* that investment in health R&D is made where there are:

- meaningful commercial markets in the developed world (e.g. medicines for HIV infection or cancer);
- global public health market mechanisms that create a commercial market (i.e. where donor organizations such as the Global Fund and Gavi provide funding for, or directly procure, products for diseases); and
- global public health market mechanisms and middle-income country interest, whereby some markets have developed as a result of self-financing and interest (e.g. for dengue or for vaccines common in global immunization schedules, such as for diphtheria and pertussis).

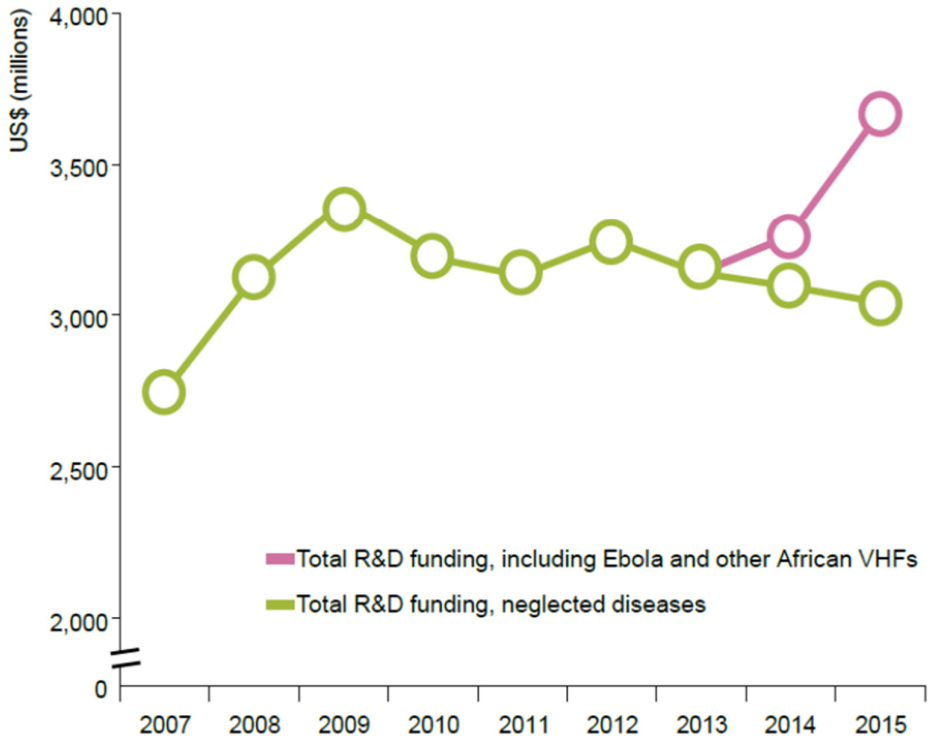
Where there is no commercial market or market-creating mechanism, R&D funding tends be scarce and fragmented. Additional resources should be identified and directed to needs-based innovation, and development approaches that rely less on IP should be explored. The GSPA-PHI, in Chapter 2, states that, while IP is an "important incentive for the development of new health care products", it does not, on its own, "meet the need for the development of new products to fight diseases where the potential paying market is small or uncertain".

The concentration of limited R&D resources on HIV, tuberculosis and malaria is understandable, as they are three main causes of mortality from infectious diseases, but it raises questions about the priority to be assigned to R&D on other diseases. Overall, global resources should be increased and diversified, and thought should be given to allocating those resources in alignment with public health-defined R&D priorities for diseases that mainly affect developing countries.

3.3 Funding and coordination of health research and development

The picture of new funding for R&D since 2008 is a mixed one. According to the most recent G-Finder survey, global R&D investment in neglected diseases reached US$ 3.67 billion in 2015 (Fig. 1); however, US$ 631 million of that sum were accounted for by investment in R&D for viral haemorrhagic fevers, which were first included in the 2014 survey in response to the outbreak of Ebola virus disease. When spending on viral haemorrhagic fever-related R&D is excluded, only US$ 3 billion were invested in 2015, down from US$ 3.4 billion in 2009 *(73)*. According to one estimate, total global investment in health R&D (by both the public and the private sector) in 2009 (the last year for which consolidated data are available) reached US$ 240 billion *(92)*. Furthermore, countries are far from achieving the proposed CEWG goal of committing 0.01% of their GDP for R&D on types II and III diseases. According to G-Finder, the USA came closest to achieving this goal, committing 0.007% of its GDP, followed by Ireland and the United Kingdom, which committed 0.0036%. Among the developing countries, India and South Africa committed around 0.002% of their GDP.

Fig. 1. Total funding for R&D on Ebola viral disease and other African viral haemorrhagic fevers and for neglected diseases, 2007–2015



Source: G-Finder

The sources of funding for R&D on neglected diseases are also highly concentrated. According to the G-Finder survey, 40% of all such funding is given to organizations that receive more than 80% of all funding from the United States Government. While support for R&D on neglected diseases from the USA is obviously important, over-reliance on a few funders increases vulnerability to any changes in funding policies. PDPs are strongly reliant on the Bill & Melinda Gates Foundation, which in 2015 provided more than half their funding. In 2015, the United States National Institutes of Health provided 40% of all funding for R&D on neglected disease and the Bill & Melinda Gates Foundation a further 17%; however, reductions in funding by these two organizations since 2009 have not been counterbalanced by increases in funding from other sources. In 2015, the public sector provided nearly two thirds of funding, the philanthropic sector a further 21% and industry 15%. Funding for the PDPs monitored by G-Finder decreased from a peak of US$ 657 million in 2008 to US$ 450 million in 2015 *(73)*.

There has been little substantive improvement in coordination of the use of funding, although foundations have been laid by the establishment of the Global Observatory on Health Research and Development and the Expert Committee on Health Research and Development, which should provide analyses of gaps in health R&D and advice on setting priorities and coordinating health R&D. These activities may result in improved governance of health R&D and more efficient use of resources globally, regionally and nationally.

3.4 Product development partnerships

There is some evidence of progress on sub-element 7.2, particularly in regard to PDPs (Box 5). While the contribution of these partnerships is significant, their over-dependence on a single source of

funding makes them vulnerable to changes in donor priorities and policies, and their funding has been falling. This overall review of the GSPA-PHI is therefore opportune, as it may stimulate governments to more actively ensure the sustainability of PDPs and to increase their R&D programmes. An issue of particular concern is the capacity to fund clinical trials, as most PDPs are unable to fund all those required without timely, sustainable funding.

Box 5. Product development partnerships: coming together to ensure access to innovation

PDPs have played a key role in increasing R&D on neglected diseases, using various approaches, drawing on public and philanthropic funding to share the risk and on expertise from both the private and public sectors. PDPs may address a single or multiple neglected diseases or product types. It is estimated that PDPs and other public–private partnerships provided funding for three fourths of products for neglected diseases in the pipeline (vaccines, drugs, diagnostics, vector control products) in 2015 *(72)*. PDPs can bridge the gaps between basic science and late-stage research at various points in the product development chain, from fundamental research to understand a disease, to operational research to optimize the use of new technologies in a health system *(99)*.

The Medicines for Malaria Venture (MMV), established in 1999, was one of the first PDPs. As it does not have the capacity to conduct early-stage development projects, MMV relies for financing and in-kind contributions (i.e. laboratories and expertise) on its extensive network of partners, which comprises more than 400 pharmaceutical and academic institutions and partners in countries endemic for malaria in 55 countries. It allocates resources to the most promising projects, coordinates various stages of R&D and manages project portfolios. The MMV and its partners have developed six new medicines: a child-friendly formulation of artemether–lumefantrine, an artesunate injection for the treatment of severe malaria, dihydroartemisinin–piperaquine, a paediatric formulation of pyronaridine–artesunate and sulfadoxine–pyrimethamine–artesunate–amodiaquine combination therapy for the prevention of seasonal malaria, which have received WHO prequalification with the support of MMV. The Venture has also assumed stewardship of two approved artemisinin-based combination therapies developed within the Drugs for Neglected Diseases initiative and its partners: artesunate–amodiaquine and artesunate–mefloquine *(100)*.

An example of the ability of PDPs to attract broad collaboration for a successful outcome is the Meningitis Vaccine Project, initiated in 2001, which was coordinated by WHO and PATH (an organization for innovation in health based in Seattle (WA), USA) with substantial funding from the Bill & Melinda Gates Foundation. A consortium of academics and scientists in the Netherlands and the USA developed a new conjugate vaccine for use in the "meningitis belt" in Africa, and transferred the technology to the Serum Institute of India, which agreed to manufacture the vaccine at a target price of US$ 0.50 per dose. African scientists contributed to the design of study protocols and conducted the clinical trials. Canada assisted the Indian National Authority in obtaining regulatory approval, and WHO prequalified the vaccine by accelerated procedures. The vaccine was made available in record time at one tenth the cost of most new vaccines. Since the start of vaccination at the end of 2010, more than 230 million people in 16 countries have been vaccinated against meningococcal meningitis serogroup A. With the added impact of herd immunity, the recurring outbreaks of meningitis A that devastated 26 African countries for decades have now been virtually eliminated *(101)*.

While most prominent PDPs still address only neglected diseases, the urgent need for new antibiotics has resulted in new partnerships. The Global Antibiotic Research and Development Partnership, a joint venture between WHO and the Drugs for Neglected Diseases initiative, was launched in May 2016 to respond to the WHO global action plan on antimicrobial resistance. The public and private sectors both work to develop new or improved antibiotics for bacterial infections whose bacteria are resistant to existing antibiotics or in which drug resistance is emerging. The Partnership secured € 6.5 million in seed funding, and a further € 56 million were raised from the Netherlands, South Africa and Switzerland; the German Government, Luxembourg, the United Kingdom and the Wellcome Trust provided €51 million *(102)*. The Partnership's business plan is to secure €270 million over the next 7 years for the introduction of up to four treatments and for bringing four candidate drugs to preclinical and clinical development *(103)*.

Another new initiative is the Combating Antibiotic-resistant Bacteria Biopharmaceutical Accelerator, a partnership between the Biomedical Advanced Research and Development Authority of the United States Department of Health and Human Services and the Wellcome Trust. The Accelerator was launched in July 2016 to fill the gap in R&D for new medicines and other health products for the diagnosis and treatment of drug-resistant infections; it has committed itself to award up to US$ 455 million to suitable R&D projects over 5 years. So far, it has a pipeline of 18 promising research projects, including for eight new classes of antibiotic *(104)*.

Another challenge is the development of health products for diseases such as Ebola virus disease, Middle East respiratory syndrome, severe acute respiratory syndrome and Zika virus disease. These diseases are neglected in market-driven models of R&D because they occur sporadically, unpredictably and often in resource-limited countries with poor health systems. Building on the experience of the Ebola virus disease outbreak in West Africa in 2014 and the testing of a vaccine against the disease, WHO has designed an "R&D blueprint" to improve preparedness for rapid development of health products for use in outbreaks *(105)*. The blueprint lists diseases that are likely to cause epidemics in the future, R&D "roadmaps" and profiles of the vaccines, medicines and diagnostics that would be required to address the diseases. So far, four product profiles have been prepared for vaccines and diagnostics for addressing Zika, Nipah and Lassa fever viruses. The standards will guide the research of WHO's partners and ensure that all are working on the basis of the same standards for quality, safety and efficacy. WHO has also established an emergency procedure within its Prequalification of Medicines Programme for the rapid assessment of new health products during public health emergencies, and has called on companies to develop technologies to expedite the development and production of health products required during epidemics. Several dozen valid proposals have been received.

One of the partners in this initiative is the Coalition for Epidemic Preparedness Innovations, which was launched in January 2017 with initial funding of nearly US$ 500 million *(106)*. In its preliminary business plan for the period 2017–2021, the Coalition stated that it would address the barriers to the development of vaccines for use in epidemics and provide safe, effective, affordable vaccines to contain outbreaks at the earliest possible stage. It plans to provide at least four candidate vaccines against two or three priority pathogens to the stage of proof-of-concept within 5 years, to allow testing of clinical efficacy in the initial stages of a potential outbreak and to build technical and institutional platforms to accelerate R&D on known and unknown emergencies due to pathogens. Another partner in the WHO blueprint initiative is the Global Research Collaboration for Infectious Disease Preparedness, a network of research funding organizations *(107)*.

3.5 Alternative models of funding health research and development

Sub-element 5.3a of the GSPA-PHI calls for stakeholders to

> explore and, where appropriate, promote a range of incentive schemes for research and development, including addressing, where appropriate, the delinking of the costs of research and development and the price of health products, for example through the award of prizes, with the objective of addressing diseases that disproportionately affect developing countries.

A number of relevant initiatives are currently under way, funded by a variety of mechanisms, which can be broadly categorized as "push" and "pull" *(108)*.

"Push" mechanisms comprise subsidies or funding for R&D, often in the form of grants or tax relief, which are given regardless of the results of the research. Examples include the European and Developing Countries Clinical Trials Partnership 2, an international partnership that provides grants and additional support for collaborative research to accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics for use against poverty-related and neglected infectious diseases in sub-Saharan Africa, particularly in phase II and III clinical trials. Since 2003, the

Partnership has funded 17 grants for treatment of HIV infection and for R&D of malaria vaccines and treatments, tuberculosis diagnostics and treatments for some neglected tropical and other diseases *(109)*.

The Global Health Investment Fund of US$ 108 million provides financing for the development of drugs, vaccines, diagnostics and other health products for diseases that disproportionately burden developing countries *(110)*. Launched in 2012, the Fund brings together stakeholders in public and private sectors to support late-stage development of products for neglected diseases, with both financial returns and a measurable social impact. The Fund is financing a number of projects, including the development and use of an oral vaccine against cholera, and millions of doses are being delivered to countries such as Malawi, Nepal and Somalia; one million doses were delivered to Haiti in late 2016 as part of relief after the passage of Hurricane Matthew *(111)*.

"Pull" mechanisms offer rewards for the development of health products with either a particular target product profile or for reaching a specific milestone in R&D (e.g. a phase 1 trial). The rewards may include incentives such as prizes or "advance market commitments". As the initial risk of any project is borne by the developer, such commitments are an incentive to maximize efficiency and to adhere to the requirements of the funder for efficacy; the funder is liable only when the specified target is met *(112)*. One drawback of pull mechanisms is that the inherent financial risk and uncertainty may deter participation, particularly by smaller companies that lack the resources to move from early-stage research to late-stage clinical trials. Other difficulties are determining the size of the prize that will motivate developers while maintaining cost-effectiveness and defining drug characteristics that are neither perversely specific nor too general. An effective pull system requires a government that is willing to stand by long-term guarantees *(113)*.

Interesting initiatives based on a pull mechanism include the Longitude Prize, launched at the G8 Summit in 2013, which offers a £ 10 million prize for the organization that develops the best point-of-care diagnostic test for bacterial infections. The test must be accurate, rapid, affordable, easy to use and available to everyone in the world. It should indicate when antibiotics are required and, if they are, which ones should be used *(114)*. Currently, 239 teams in 41 countries are competing. In December 2016, up to £ 25 000 in seed funding were granted to 12 teams in India, the United Kingdom and the USA to advance their work *(115)*. These groups are reported to be working on various technologies, from nanosensors to gene detectors to lasers, with the same goal: to find a tool that will radically transform the way people access antibiotics and help to reduce the growing threat of antibiotic resistance.

3.6 Management of intellectual property

Element 5 of the GSPA-PHI addresses the issues of IP and access, and sub-element 5.1 calls for "information sharing and capacity building in the application and management of intellectual property with respect to health-related innovation and the promotion of public health in developing countries". Action 5.1d calls for stimulation of collaboration among relevant national institutions and government departments, as well as among national, regional and international institutions, to promote the sharing of information relevant to public health.

After adoption of the TRIPS Agreement, which extended pharmaceutical patent protection to all WTO members, it was expected that R&D on health in developing countries would increase and that some of the countries would contribute new medicines, particularly to address the diseases that prevail in the developing world *(116)*. This has not been the case. While some countries, notably India *(117,118)*, have recently initiated significant R&D, there is no evidence that the adoption of the TRIPS Agreement changed the situation *(119)*.

A number of collaborative and open-source initiatives are under way *(108)*. Collaborative initiatives bring together public research institutions and/or members of the private sector, including biotechnology and pharmaceutical companies, in a network, consortium or partnership. The

exchange of information within a collaborative initiative is often regulated by material transfer agreements and restricted to the collaborating entities.

Open R&D initiatives apply the principles of open source, open access, open data or open knowledge and make resources such as IP licences and data freely available. Examples of open initiatives include the Malaria Box, which was launched in 2011 by MMV to catalyse the development of drugs against malaria and neglected diseases *(120)*. The Box, containing 400 compounds that are active against malaria (many of which are patented), was made available to researchers upon request, free of charge, until December 2015. In return, they were asked to share their findings in the public domain. About 200 research groups around the world received the Box. After the success of the Malaria Box, MMV was awarded a grant from the Bill & Melinda Gates Foundation to design the Pathogen Box, which was launched in 2015 *(121)*. This Box also contained 400 compounds for free distribution on request, but this time the compounds were active against one of several neglected disease pathogens. Researchers who received a Pathogen Box were asked to share the data generated in the public domain within 2 years, creating an open, collaborative forum for research on drugs for neglected diseases. Open-source approaches are not a panacea for R&D for new technologies for neglected diseases, as they depend heavily on grants for funding and must attract enough interested researchers to maintain momentum.

3.7 Capacity-building for research and development in neglected diseases

Building capacity for R&D is essential for needs-based innovation. Element 3 of the GSPA-PHI (building and improving innovative capacity) highlights capacity in science and technology, local production of pharmaceuticals, clinical trials, regulation, IP and traditional medicine as areas for investment.

Like other aspects of the GSPA-PHI, monitoring capacity-building for R&D in neglected disease is difficult. The indicator used by the WHO Global Observatory on Health Research and Development is the number of full-time health researchers, which is considered a broad proxy for research capacity. The indicator is monitored by UNESCO. In the 60 countries that reported for the most recent year since 2010, there were 3524 full-time health workers in high-income countries, 885 in upper–middle-income countries, 53 in lower–middle-income countries and 10 in low-income countries, indicating a significant disparity in the numbers of health researchers by country income group.

Most of the main funders of R&D on neglected diseases conduct capacity-building. For example, the Drugs for Neglected Diseases initiative has, since its inception in 2003, integrated capacity-strengthening into its projects through knowledge-sharing and technology transfer. The objectives of the Initiative are to increase the chances of registration, uptake and sustainable access to new treatments for neglected diseases and, ultimately, transfer of ownership to the countries in which the disease is endemic *(122)*. The Wellcome Trust funds a number of capacity-building initiatives, including the African Institutions Initiative, which supports seven consortia, comprising 54 institutions across the continent and 20 institutions in Europe and North America. The aims are to increase scientific research in under-resourced environments, support areas of science that could contribute to improving the health of people and livestock and support international networks and partnerships for the health problems of resource-poor countries *(123)*. The United States National Institutes of Health support international research and training programmes to address global health challenges and have financed the training of over 5000 researchers in developing countries *(124)*.

Private sector companies also support R&D capacity-building, sometimes to gain access to attractive markets. For example, foreign companies are more likely to license technologies to Chinese firms and research institutes than to firms in other developing countries because of the size and dynamism of China's pharmaceuticals market and Chinese policies on foreign investment. China is thus a focus of private sector R&D capacity-building, along with Brazil. Companies are also building R&D capacity in Kenya and South Africa. Some private sector companies, such as GSK, Merck and Novartis, are also supporting R&D capacity development for neglected diseases *(125)*.

GSPA-PHI sub-element 2.2f calls for building capacity to conduct clinical trials and to find public and other sources of funding for trials, to stimulate local innovation. Researchers in developing countries outside the academic or public sector have limited opportunities to build the skills required, and, therefore, not enough researchers in these countries conduct clinical research for neglected diseases. To address this issue, the European and Developing Countries Clinical Trials Partnership and the Special Programme for Research and Training in Tropical Diseases at WHO are implementing a fellowship scheme to support researchers who wish to obtain these skills and to take advantage of synergies among researchers and clinical staff, pharmaceutical companies, PDPs and research institutions *(126)*. The Partnership is involved in initiatives to accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics for HIV/AIDS, tuberculosis and malaria and other poverty-related infectious diseases in sub-Saharan Africa. It collaborates in the TRUST ethics project, a global ethics consortium funded by the European Union, which supported development of the San code of research ethics by the South African San Institute and San Council in collaboration with three San groups. The aim of the code, published in March 2017, is to prevent exploitative research in San communities *(127)*. Other initiatives in southern Africa are described in Box 6.

Box 6. Building R&D capacity in southern Africa

Sub-Saharan Africa has hosted many R&D capacity-building projects in the past few years. One example is the Trials for Excellence in Southern Africa, a collaboration involving 10 southern African research institutes and universities conducting research on HIV/AIDS, tuberculosis and malaria. Supported by the European Union and the European and Developing Countries Clinical Trials Partnership through the South African Medical Research Council, the network improves research coordination and links with local and international partners. Through capacity development, the collaboration has upgraded a number of sites, initiated several studies and trained clinicians, scientists and laboratory technicians. It supports the part- or full-time work of 40–50 scientists, clinicians, nurses and laboratory technicians *(128)*.

The South African HIV Vaccine Trials Network AIDS Early Stage Investigator Programme was established in 2010 by the HIV Vaccine Trials Network with support from the United States National Institute of Allergy and Infectious Diseases and the Fogarty International Center. This peer-reviewed programme is coordinated by the Desmond Tutu HIV Centre at the University of Cape Town. It builds research capacity and strengthens the contributions of young South African investigators to research on an HIV vaccine in a structured research, mentorship and PhD programme.

The South African Medical Research Council Strategic Health Innovation Partnerships programme, formed as a health technology PDP in 2013, manages and funds multidisciplinary, multi-institution product R&D and innovation projects, from discovery to proof-of-concept. It leverages local and international funding by acting as a central conduit for foreign institutions that wish to form partnerships with South African research agencies. In partnership with local universities, science councils and the private sector, innovation initiatives are being managed on HIV, tuberculosis, malaria, noncommunicable diseases and medical devices *(129)*.

The Global Health Innovation Accelerator is a South African centre led by the Strategic Health Innovation Partnerships unit at the South African Medical Research Council and by PATH. The aim of the Accelerator is to advance the most promising technologies for addressing the health needs of low-resource communities. It connects scientific and technical experts, funders and networks of global partners with local scientists and innovators to accelerate product development and introduction. The primary initial focus is on medical devices, diagnostics and other health tools *(130)*.

WHO's work includes the International Clinical Trials Registry Platform, established in 2005, which links clinical trial registries in a single point of access to information on all trials globally *(93,131)*. Registration of all intervention trials ensures that decisions about health care are based on all the available evidence, including evidence of inefficacy. Registration also ensures that researchers and funding agencies avoid unnecessary duplication of effort and facilitates the identification of gaps in clinical trials research. Registries in which data are checked during registration may improve the quality of clinical trials by early identification of potential limitations (such as problematic randomization methods). Regional initiatives include the Pan African Clinical Trials Registry, which

seeks to increase clinical trial registration in Africa by raising awareness of the importance of registering trials and by supporting registration *(132)*. The Registry is managed by the South African Cochrane Centre, a unit of the South African Medical Research Council and is the only African primary registry in WHO's registry network. It fulfils global requirements for prospective registration of all trials before publication by providing an open-access platform for registration free of charge and a searchable electronic database of trials that are planned and in progress. The registry works in collaboration with the Cochrane Infectious Disease Group, the Cochrane HIV/AIDS Group and WHO. Other countries have also launched publicly accessible clinical trial registries *(133)*.

This review of the GSPA-PHI provides an opportunity to emphasize the importance of increasing capacity for conducting clinical trials as a part of overall capacity development for innovation.

3.8 Conclusion

The R&D landscape described here gives contrasting impressions; however, the general picture almost 10 years after adoption of the GSPA-PHI is disappointing, particularly as its main objective is: "to promote research and development focusing on Type II and Type III diseases and the specific research and development needs of developing countries in relation to Type I diseases". Although the size of the product pipeline for these diseases increased somewhat during the past decade, neglected diseases continue to be neglected. Funding has not increased sustainably since 2008, in spite of the recent increase related to the outbreak of the Ebola virus disease.

While progress in health R&D has been limited, there have been some positive changes. One of the most striking is the profusion of active R&D funding initiatives, notably in the form of PDPs. According to the G-Finder survey, PDPs now account for 58% of the products for neglected diseases in the pipeline. They are also leading the response to AMR. Their capacity to deliver end products will, however, depend on addressing their financial vulnerability.

Another striking change is the increasing role of the private sector, beyond its participation in PDPs. Industry investment in R&D for neglected diseases reached new heights in 2015, and its share of global funding is now comparable to that of the Bill & Melinda Gates Foundation. As global sales of prescription drugs increased from about U$S 600 billion in 2008 to more than U$S 800 billion in 2016 *(134)*, however, industry's investment in R&D for neglected diseases has decreased relative to income. As far as the limited data show, countries' investment has also not increased, despite increases in GDP (and health budgets) in some countries during the same period *(73)*.

A greater focus on needs-based innovation will be crucial to improve public access to medicines and other health products. This is, however, only part of the picture, as recognized in the GSPA-PHI, which includes numerous references to broader issues of access to both newly developed and existing products, particularly under element 6. We turn to these issues in the next chapter.

Chapter 4.

Improving access to health products in the context of the global strategy and plan of action

4.1 Introduction

An underlying assumption of the GSPA-PHI is that innovation is of little value unless people have access to the products it generates. Element 6 of the Strategy relates entirely to improving delivery of, and access to, medicines and health products. It covers a wide range of topics, including national policy on IP, the quality and use of essential health products, health workforce training and procurement and supply chain management.

Access to all medicines and technologies at all prices is a challenge in some contexts, regardless of whether the product is patented or not. The extent and nature of the challenge depends on factors such as the size of the market, regulatory barriers, and even corruption. The critical factor, however, is whether the market is competitive.

As noted in Chapter 2, there are no comprehensive data for assessing the current state of access to medicines and health products. Efforts have been made to improve the monitoring of availability and prices, but better monitoring of universal health coverage and achievement of the SDGs is required *(135,136)*. Progress towards achieving SDG 3.8 on universal health coverage is monitored by measuring two indicators: coverage with financial protection and coverage with essential health services, the latter measured against an index of 16 indicators of health services, including access to interventions for HIV infections, tuberculosis and malaria. Coverage with antiretroviral agents for HIV infection, bednets for malaria and treatment for tuberculosis has increased considerably since 2000, reflecting significant increases in dedicated resources. Coverage with interventions for maternal, newborn and child health has also increased, notably with a vaccine against diphtheria, tetanus and pertussis, and there has been a significant improvement in access to anthelminthic and antimicrobial medicines for certain neglected tropical diseases *(135,137)*.

The limited data available for the period 2007–2014, from 26 surveys conducted in developing countries, indicate, however, that the median availability of generic medicines was only 58% in public sector facilities and 67% in the private sector *(138)*. There is concern that, as donors withdraw support for countries as their per capita income increases, access to health products may deteriorate *(139)*. Meanwhile, rising prices, especially for new medicines, are a problem for all countries, regardless of their income. Recently developed directly-acting antiviral agents to treat hepatitis C are a case in point. Their prices have decreased in the past few years as more competitors have entered the market, notably in some developing countries; however, a global analysis of information on the public price of sofosbuvir and the fixed-dose combination ledipasvir–sofosbuvir in 30 countries in 2015 showed that the total cost of treating all patients with hepatitis C with either medicine would represent at least one tenth of the annual cost of all medicines in those countries. In countries where prices are high and the burden of disease is great, the total cost of treating all infected patients would be greater than the cost of all other medicines together *(83)*. The high price of drugs used in oncology is also a concern *(140)*, as are the prices of drugs for “orphan” diseases *(141)*. As a result, access is now a concern in both developed and developing countries *(142)*.

A comprehensive health-systems approach is required to improve access, addressing all stages of the chain, from needs-based R&D and innovation to effective regulation, manufacturing processes and systems that ensure high-quality products, public health-oriented IP and trade policies, effective selection, pricing and reimbursement policies, integrity and efficiency in procurement and supply and appropriate prescribing and use. Access also depends on the degree to which countries rely on prepayment, pooling of resources and sharing of financial risks *(143)* rather than out-of-pocket payment to fund health services. This topic is not addressed in the GSPA-PHI.

4.2 Manufacturing

The production of high-quality medicines and health products is essential for achieving the goals for access. The problems include insufficient access to technologies, weak physical infrastructure, scarce appropriately trained technical staff, and inadequate quality control and regulation mechanisms. These problems are often compounded by a dependence on imported raw materials, including active pharmaceutical ingredients, and markets with weak, unpredictable demand. Moreover, regulatory authorities in many countries lack the capacity to ensure that manufacturers comply with good manufacturing practices, for instance according to WHO guidelines *(144)*.

In element 3 of the GSPA-PHI, local production of pharmaceuticals is identified as an important area for investment, and element 4 calls for promotion of the transfer of technology and production of health products in developing countries. The Local Manufacturing Initiative of WHO and partners supports local production of good-quality health products in developing countries, particularly in Africa *(145)*. The goal is to increase access to essential medicines, vaccines, medical devices, in-vitro diagnostics and blood products. Local production is also supported by other international organizations, such as UNIDO and UNCTAD. The Initiative has identified the potential benefits of extending local production and certain challenges, such as a lack of capacity to develop policies and regulations and a lack of implementation and coordination activities, including good governance. A good example of stakeholder collaboration is the African Union's Pharmaceutical Manufacturing Plan for Africa and its business plan, which outline a comprehensive approach to aligning policy on national health and industrial priorities and capacity-building in pharmaceutical manufacturing *(146)*.

Countries in other regions have also made significant advances in local production. For example, Brazil has initiated a Growth Acceleration programme and the Greater Brazil Plan to increase domestic production of innovative drugs, which promotes public–private partnerships for technology transfer to public pharmaceutical laboratories for the development of similar biotherapeutic products *(147)*. Cuba *(148)*, Ethiopia *(145)*, India *(149)* and the Russian Federation *(150)* are also promoting local production, and China is supporting local production as part of its universal health coverage programme *(151)*.

Under sub-element 6.2, the GSPA-PHI calls for countries to comply with good manufacturing practices for the safety, efficacy and quality of health products. This includes strengthening WHO's Prequalification of Medicines Programme, which has substantially contributed to improving access to high-quality medicines in developing countries, notably by ensuring that medicines purchased by or through international procurement agencies such as UNICEF and the Global Fund meet acceptable standards of quality, safety and efficacy. The programme was initially created to ensure stringent assessment of low-cost treatments for HIV infection, tuberculosis and malaria; however, its remit has been extended to include prequalification of active pharmaceutical ingredients, laboratories for testing drugs, vaccines and diagnostics. This year, WHO initiated a pilot project for prequalifying "biosimilars", a step towards making some of the most expensive treatments for cancer more widely available in developing countries *(152)*. The Prequalification Programme also covers in-vitro diagnostics for priority diseases and assesses their suitability for use in resource-limited settings. It conducts training programmes in which regulators in developing countries learn from those in developed countries, with subsequent inspections by experts. The programme also provides rotation fellowships at WHO *(101)*.

4.3 Intellectual property

The manufacture of medicines and health products in a country requires ownership of, or a contractually licensed right, to the relevant IP. This is reflected in element 5 of the GSPA-PHI, which refers to full exploitation of the flexibilities of the TRIPS Agreement, including the right of governments to grant compulsory licences (see Box 3, above). As discussed in Chapter 2, a number of developing countries have taken advantage of the flexibilities since adopting the GSPA-PHI,

including post-grant flexibilities (such as compulsory licensing) and pre-grant flexibilities, such as patentability requirements designed to curb the practice of "evergreening", which is used to extend the market exclusivity of patented products for commercial purposes. A legal framework for legitimate use of the flexibilities of the TRIPS Agreement is also relevant for developed countries in which there are increasing limitations on ensuring the delivery of high-priced medicines. The resolution of the European Parliament on improving access to medicines *(142)* states that the European Patent Office and Member States should grant patents on medicinal products only if they strictly fulfil the patentability requirements of "novelty, inventive step and industrial applicability", as stated in the European Patent Convention.

One strategy for improving access is enacting appropriate patent legislation and supporting capacity-building in this area. Countries can also develop and implement trade policies that encourage better access to medicines. A significant development is the extension of the provision in TRIPS that releases least-developed countries from the obligation of applying pharmaceutical patent protection until 2033 *(153)*. Most least-developed countries have not taken advantage of this exemption, and they might thus wish to review their policy.

WHO work in IP includes promoting trilateral collaboration with WTO and WIPO for training and capacity-building and the publication of a joint study on promoting access to medical technologies and innovation *(154)*. WHO has also published a report on the role of IP in local production, which provides guidance for policy-makers in countries with industries that produce generic products on designing a conducive IP system *(155)*. It stresses the importance of good understanding of patent laws and patent systems by local producers and the availability of competent IP professionals and a transparent, fair, efficient legal system to allow such policies to flourish.

4.4 Regulation

Robust processes for regulatory approval are essential to ensure access to safe, effective, high-quality medicines and health products. The GSPA-PHI calls for strengthening regulatory capacity in developing countries to promote both innovation and access. While some countries have acquired significant technical and institutional capacity in regulation, the authorities often lack the expertise and resources to review new health tools effectively. Possible temporary or permanent solutions are to grant marketing approval on the basis of previous decisions by "stringent regulatory authorities"[3], sometimes called "approval by reference", or on the basis of previous assessments by the WHO Prequalification of Medicines Programme, as suggested in the WHO Collaborative Procedure for Accelerated Registration *(156)*.

The WHO Department of Essential Medicines and Health Products has designed a capacity-building programme to strengthen regulatory bodies by providing technical advice, training and seminars and has begun to adopt more innovative, effective approaches to strengthening regulatory systems *(157)*. So far, 127 national regulatory authorities have benefited from capacity-building with the support of the department. The department also supports regional and subregional regulatory harmonization initiatives, centres of excellence and training networks *(158)*.

Access to medicines and health products may be compromised by the complexity of the approval process. Regulatory approval must be secured in each country in which a product is intended for use, whereas each national regulatory agency may have different requirements, and there are often long delays before approval. It has been estimated that the total time to registration of medicines and vaccines in developing countries (including approval by the country of manufacture, WHO prequalification and approval from the local regulatory agency) is 4–7 years after completion of

[3] The national drug regulatory authorities that are members, observers or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use are considered "stringent regulatory authorities" as per the Global Fund quality assurance policy.

phase-3 trials and assembly of a dossier for marketing application *(159)*. In developed countries, the average time to product approval is much shorter. In the USA, for example, industry reported that the average time between filing and approval is 1.6 years; cancer drugs generally require the shortest review time (1.1 years) and neurological drugs the longest (2 years) *(160)*.

A number of initiatives to harmonize regulatory processes have been launched at regional and sub-regional levels. They include the African Medicines Regulatory Harmonization initiative, which has intervened to harmonize regulations in the five countries of the East Africa Community and in the 15 countries of the Southern African Development Community through the Zazibona project *(161)*. The Association of Southeast Asian Nations Pharmaceutical Product Working Group is harmonizing the regulation of medical products within member countries *(162)*, and the Pan American Network for Drug Regulatory Harmonization supports countries in the Americas *(163)*.

4.5 Selection of medicines and medical devices

Effective selection and procurement of essential medicines and health products is key to improving access, as reflected in element 6 of the GSPA-PHI, which calls for the production and introduction of generic versions of medicines and, in particular, of essential medicines in developing countries. The same element calls on countries to frame and implement policies to improve access to safe, effective health products, especially essential medicines, at affordable prices, consistent with international agreements.

WHO has published a model Essential Medicines List every two years since 1977, to assist countries in selecting medicines for their health systems. The List began as a core component of primary health care in resource-constrained settings; the aim was to ensure the provision of basic, indispensable medicines *(164)*. The focus shifted in the late 1990s, and, in 2002, WHO modified its definition of "essential medicines" from those "of utmost importance, and are basic, indispensable and necessary for the health and needs of the population" to "those that satisfy the priority health care needs of the population". The second definition includes comparative cost-effectiveness as a criterion for selection to facilitate the introduction of more expensive medicines *(165)*. In 2015, the Expert Committee responsible for updating the List called for action to promote equitable access to several new, highly effective medicines, which were the new directly-acting antiviral agents to treat hepatitis C, 16 medicines for cancer and five new medicines for tuberculosis *(166)*. The List was again revised in 2017, when the Expert Committee grouped antibiotics into three categories, "access, watch and reserve", to ensure that antibiotics are available when needed and that the right antibiotics are prescribed for the right infections *(167)*.

The selection of medicines and health products has also been facilitated by greater use of HTAs. These are not mentioned in the GSPA-PHI but have become an integral part of product selection in recent years and a topic of interest for Member States, as reflected in World Health Assembly resolution WHA67.23 *(168)*. HTA is not used widely in developing countries. A recent survey found that the main impediment to strengthening HTA capacity was lack of training of human resources *(169)*.

A WHO guideline on pharmaceutical pricing policies *(170)* acknowledges the lack of HTA capacity in developing countries but describes other ways in which HTA can be approached, from full appraisal – the most sophisticated approach, demanding the most technical resources – to a less resource-intensive evaluation of published HTA reports for local use. WHO provides information for countries with limited capacity but recommends that they use a stepwise approach in developing legislative and technical capacity to take full advantage of HTA in pharmaceutical price setting. Capacity can also be developed in national academic institutions with expertise in HTA, which can serve to provide external reviewers and train a future generation of assessors.

4.6 Price negotiation and purchasing

Once countries have determined the medicines and health products they require, they must set the price they should pay. Governments tend to rely on one of three approaches to obtain affordable medicines: negotiation, regulation and strategic procurement *(171)*. Negotiations are usually conducted on the basis of external reference pricing, cost-plus pricing and value-based pricing (Box 7).

Box 7. Bases for negotiating the price of medicines

External reference pricing: Also known as international reference pricing, this is the simplest approach to setting prices. It involves using the price of a pharmaceutical product (generally the manufacturer's selling price or list price, also referred to as the ex-factory price) in one or several countries to derive a reference price. The lowest reference price is usually the average or the average of the lowest prices in selected countries. External reference pricing is the most common method used in European countries and is also widely used outside Europe *(171)*.

Cost-plus pricing: This involves setting retail prices at a level that takes into account the production cost of a medicine, an agreed part of the cost of promotion, and the charges and profit margins accrued along the supply chain. One of the disadvantages of cost-plus pricing is that reliable information about the costs and margins of companies is required for the calculations.

Value-based pricing: This involves the use of a policy or strategy designed to link the price and/or approval of a pharmaceutical product to the value of the product *(172)*. The basis of this approach is that the price of goods should reflect the value to the buyer rather than the actual cost of production plus a margin, as in cost-plus pricing. The question therefore is how to define and measure the value of a product. Various definitions of value are used globally, reflecting not only different technical approaches and health care systems but also different priorities and concerns.

Lack of transparency about the costs of R&D and manufacturing of medicines makes it difficult for purchasers to determine a "fair" price, i.e. a price that permits a reasonable return on investment for the developers and an affordable price for buyers *(173)*. They thus usually rely on external reference pricing, which may be unreliable because of the lack of transparency about actual prices. WHO has established the "global price reporting mechanism", which provides data on pricing and procurement of drugs for HIV infection, tuberculosis and malaria, and now on new treatment for hepatitis C *(174)*. The Secretariat has established a comprehensive web platform for data on vaccine products, prices and procurement ("V3P") in order to increase price transparency and inform decisions on the introduction and use of vaccines *(175)*.

Countries should use a combination of pricing policies that suits their circumstances. Pricing policies should be transparent and supported by appropriate legislative, technical and institutional frameworks. The regulation of prices, if considered appropriate, must be monitored closely if it is to be effective. For strategic procurement, it is generally accepted that pooled procurement, or "joint purchasing", can reduce the prices of medicines, not only by increasing monopsony (a market situation in which there is only one buyer) but also by increasing the volume of a product included in a tender, opening the way to economies of scale for the seller and bulk purchase discounts for the buyer. The importance of strategic procurement is highlighted in the GSPA-PHI, which encourages pooled procurement of health products and medical devices, where appropriate, as one means of improving delivery and access (sub-element 6.1). WHO has long supported coordinated international and national efforts to achieve system-wide, sustainable improvements in procurement practices *(176)*.

Collective procurement became increasingly common during the past decade, and a number of governments have achieved significant price reductions. For example, in 2008, the Government of Mexico created a coordinating commission for negotiating the prices of patented medicines on Mexico's essential medicines list. The accumulated direct savings in 2008–2011 relative to the year

before establishment of the commission were reported to have reached US$ 355 million *(177)*. At the regional level, notable procurement initiatives include the Pan American Health Organization Strategic Fund *(178)* and the Pharmaceutical Procurement Service of the Organization of Eastern Caribbean States (formerly the Eastern Caribbean Drug Service) *(179)*. Pooled procurement is also used by Gavi, the Global Drug Facility, the Global Fund and others. Global tenders for specific products have increased the availability and affordability of generic medicines. For example, the Global Drug Facility achieved a 26% reduction in the cost of treating a patient with multidrug-resistant tuberculosis for 24 months, with the costs of second-line drugs decreasing from US$ 7890 in 2011 to US$ 5822 in 2013 *(180)*.

The success of procurement strategies depends mainly on the existence of diverse sources of high-quality supplies that are ready to compete in order to obtain an order. Competitive bidding is not possible when there is a single supplier or when potential suppliers have been driven out of the market by too low prices. Encouraging sustainable competition through procurement strategies was discussed at WHO's Fair Pricing Forum, where participants pointed out that "winner-takes-all" tendering (in which contracts are usually awarded to the lowest bidder) can drive manufacturers of higher-quality products out of the market, or incite them to switch to more profitable production lines. In some countries, including Italy, tenders are split 70% and 30%, the 30% being distributed among the losing bidders *(173)*.

4.7 Supply chain

Element 6 of the GSPA-PHI calls for effective supply chain management to improve delivery and access. Bottlenecks in the supply chain continue to be major obstacles to access to medicines and health products *(181)*, and developing countries face enormous challenges in ensuring effective, sufficient provision of health commodities because of unreliable transport and transport infrastructure, inadequate storage facilities and a lack of an appropriately trained workforce for supply chain management. Part of the problem is the increasing pressure on supply chains caused by increased investment in global health initiatives for addressing priorities such as HIV/AIDS. Although some of the funding is used to improve the supply chain, the volume of medicines, vaccines, bed nets and diagnostic and laboratory materials flowing through supply chains has increased enormously *(182)*.

There has been growing international recognition of the role of supply chains in health systems strengthening during the past decade in global health initiatives, bilateral agencies and also pharmaceutical companies *(183)*. Countries facing significant demographic, epidemiological and economic change are also beginning to acknowledge the value of investment in improving their health care supply chains, giving rise to new approaches, including the integration of supply chains for several diseases. Such integration requires precise coordination, as the wide variety of product supply chains are managed by different agencies, products are transported to multiple delivery points through specific supply chains, and many have specific requirements such as a controlled temperature *(184)*. A number of countries have made significant progress by investing in supply chain management and health systems strengthening, including Cambodia, the Democratic Republic of the Congo and Rwanda, where performance-based payment systems are used to rapidly improve access to health care and the quality of that care *(185)*.

4.8 Prescribing, dispensing and rational use

Initiatives to improve the manufacture and distribution of medicines and health products will do little to improve access without comparable efforts on the demand side to ensure appropriate prescription, dispensing and rational use. These crucial issues are barely mentioned in the GSPA-PHI.

Given the importance of rational use (including dispensing and prescription) for access to medicines and medical products, focus on this area could be increased. WHO has estimated that more than half

of all medicines are prescribed, dispensed or sold inappropriately and that half of all patients fail to take them correctly *(186)*. Overuse, underuse or misuse of medicines strongly affects access, as it results in waste of scarce resources and various health hazards. Recent studies concluded that the underuse of medical care that is proven to be effective and the overuse of unproven services are prevalent in all economic settings, causing suffering among millions of people and wasteful misallocation of resources for society *(187–190)*.

WHO has published guidelines on the use of antimalarial agents, contraceptives, drugs for the treatment of maternal infections and other medicines *(191)*. The Secretariat is also leading work on surveillance of the consumption and use of antimicrobial medicines and has developed a method for surveillance, for which training and surveillance began in 2016 *(192)*. A protocol for a point prevalence survey of antimicrobial use in hospitals is based on one published by the European Centre for Disease Prevention and Control, and surveys are planned for later in 2017. The work of the Centre in this area includes the management and coordination of ESAC-Net, a Europe-wide network of national surveillance systems, which provide European reference data on consumption of antimicrobial agents *(193)*.

4.9 Financing

Element 7 of the GSPA-PHI promoted sustainable financing mechanisms, particularly for R&D. Financing of delivery is not addressed. Sustainable financing to ensure access to medicines and health products is fundamental and should be a key component of the GSPA-PHI.

The most recent data indicate a levelling of external funding for health in the past few years, due to factors including the fiscal austerity policies in many countries after the 2008 financial crisis *(194)*. Examples include an almost 13% decrease in donor funding between 2014 and 2015 for the response to HIV/AIDS in developing countries *(195)*. The decreases in donor funding place pressure on governments to mobilize resources domestically; however, the most recent report from the Global Health Expenditure Database *(196)* indicates that, despite prioritization of domestic public spending on health to progress towards universal health coverage, the share of total government spending for health has increased only modestly worldwide since 1995 and has actually decreased in developing countries since 2008, falling below 10% of total expenditure in 2014.

Increased funding to ensure access to medicines and medical products is essential, but it is also vital that countries move from out-of-pocket payment towards prepayment and pooling of resources to share risk and ensure increased access. Many countries are now using general budget revenues to extend coverage of health interventions to the poor, people in the informal sector or their entire population. This shift requires that donors and countries alike refine the ways in which they target aid, and that governments increase their overall domestic resource generation through better national taxation systems that are both equitable and efficient *(136)*.

4.10 Conclusion

This overview of the current situation of access to medicines and health products was limited by the existence of only a few relevant activities and various difficulties in monitoring. Initiatives to monitor achievement of the SDGs and universal health coverage may clarify the picture, but greater focus is required on this area, notably at country level. The problems of access to medicines and other health products have not diminished since the GSPA-PHI was adopted; in fact they may have been aggravated by, for example, the development of high-cost medicines, such as biologicals, which are both essential and (for the time being) largely inaccessible.

The chapter shows that obstacles to access arise at all stages of the value chain, from mis-prioritized R&D, suboptimal IP management, inefficient regulation, substandard manufacturing, ineffective selection of medicines and medical products, suboptimal procurement and irrational prescribing and

use. Access to medicines and health products is also limited by payment systems that do not protect individuals seeking care from financial risk. Most of these issues are beginning to be addressed in various global, regional and national initiatives, often with the guidance and support of WHO. There is, however, considerable scope for more action. Lack of awareness of the GSPA-PHI (a key finding of the evaluation and a topic addressed in the next chapter) and challenges to implementation due to the design of the GSPA-PHI have undoubtedly stood in the way of achieving progress. At the same time, the absence of certain topics, such as rational use and payment systems, in the current GSPA-PHI should clearly be addressed.

Chapter 5.

Assessment of the evaluation of the global strategy and plan of action

5.1 Introduction

At the Sixty-eighth World Health Assembly, Member States decided to extend the time-frame of the GSPA-PHI from 2015 until 2022 and to undertake a comprehensive evaluation of its implementation in 2015–2016 *(197)*. The goals of the evaluation were to:

- assess implementation of the GSPA-PHI;
- identify achievements, gaps and remaining challenges;
- make recommendations on the way forward; and
- inform the programme review.

The evaluation covered the eight elements, 25 sub-elements and 108 specific actions defined in the action plan for the period 2008–2015. The evaluation was contracted to Capra International Inc., and a team of 14 people was responsible for the design, conduct and analysis of the evaluation. Input was also received from an ad-hoc evaluation management group comprised of six independent content experts and two evaluation experts from the United Nations Evaluation Group and the WHO Evaluation Office, although the nature of the input from this group was unclear. The methods were reported to be consistent with the norms and standards for evaluation of the United Nations Evaluation Group.

A mixed method approach was used, based on primary and secondary data. All Member States were invited to nominate a single focal point to facilitate data collection from all relevant government entities. Of the 194 Member States, 101 (52%) nominated a focal point, and 68 (35%) contributed to the evaluation. Data were collected in all six official languages of the United Nations system.

Relevance, effectiveness, sustainability and impact were the domains of interest. The data sources included documents, interviews with key informants, the outcomes of focus groups, three surveys (a long version to 85 participants in Member States and stakeholder groups in the GSPA-PHI, a short version to the four non-responders and a web-based public survey with 62 participants) and 15 country case studies. The case studies were selected to cover all six WHO regions and the World Bank country income groups in the countries that had appointed focal points. Only two low-income countries contributed. Of the 15 case studies, three were undertaken remotely. Survey results were reported on a two- or four-point scale (yes/no or not at all, to some extent, to a fair extent and to a great extent), stratified by income and stakeholder grouping. Overall, 69% of the data (no information on the numerator or denominator) were derived from documents, 19% from the interviews and focus groups and 12% from the surveys. The data sources appeared to be spread across income categories and stakeholder groupings (with no detail of the composition of the groups).

Stakeholders (broadly interpreted) were represented by four groups: Member States, WHO Secretariat, international organizations and others (including national research institutions, academia, regulatory agencies, nongovernmental organizations, charitable organizations, publishers and health-related industries). Data were anonymized, but the contributors to the case studies and surveys were listed.

5.2 Main findings

The evaluators constructed an overall view of the GSPA-PHI and then presented their findings by element. They used a force field analysis to identify the factors that facilitated or impeded implementation. The scores assigned by the evaluation team to the force exerted by each factor ranged from 1 (extremely weak) to 5 (extremely strong).

They proposed that positive factors for the future implementation of the GSPA-PHI would include:

- stakeholders' awareness of and support for the programme (1);
- the priority given to the health sector (4);
- prioritization and promotion of R&D needs by stakeholders (3);
- willingness to build and improve innovative capacity (3);
- willingness to improve delivery and access (3); and
- support for Member States by WHO (4).

The negative factors for future implementation of the GSPA-PHI would include:

- little awareness of the GSPA-PHI (4);
- weak building and improvement of innovative capacity (3);
- weak sustainable financing systems (2);
- lack of coordination among partners (2);
- weak monitoring and reporting systems (3); and
- weak local ownership and leadership (2).

By adding the scores, the evaluation team found that the positive factors outweighed the negative factors by a narrow margin (18 to 16). On that basis, they concluded that the positive factors should be strengthened and the negative factors reduced if the risk that the GSPA-PHI will fail is to be avoided. In addition, the evaluators presented three findings judged to be of relevance to the entire programme.

- *Awareness*: As data were derived only from the Member States that responded, awareness (and therefore impact of the GSPA-PHI) is probably overestimated.
- *Variation by income group*: The findings for several, if not all, the elements are similar: stakeholders may be aware of the GSPA-PHI, but progress in implementation varies and appears to be less in developing countries with fewer resources. The way in which each element was implemented therefore depended on the priorities and capacity of each country.
- *Attribution*: Many countries began implementing activities identified in the GSPA-PHI before 2008 or since. In either case, it is problematic to attribute any activity to the GSPA-PHI.

The evaluation then addressed the eight elements of the GSPA-PHI in a structured manner: a summary of each element; the main findings of the evaluation; observations from the country case studies; key achievements, key gaps and challenges; and three sets of recommendations, for Member States, for the WHO Secretariat and for all stakeholders, with a total of 32 recommendations: 15 for Member States, 17 for the WHO Secretariat and 10 for all stakeholders.

5.3 Analysis

Just as the evaluation was written to be forward-looking, the intent of this critique is to learn from the evaluation and thus inform the next stage of the GSPA-PHI, including plans for implementation and evaluation. The evaluation had some positive aspects, including use of mixed methods (combining qualitative and quantitative data), inclusive stakeholder involvement, detailed country case studies, detailed presentation of the data sources, survey results and recommendations stratified by stakeholder. It also had many weaknesses, some of which were recognized by the evaluators.

Selection bias, leading to a potential overestimate of awareness about and the impact of the GSPA-PHI: First, as pointed out by the evaluators, only 35% of Member States contributed, and it is likely that they were more aware of the GSPA-PHI than the non-responders. Secondly, and probably more importantly, the profiles of those who participated suggest that they were self-selected by familiarity or geographical proximity to WHO rather than because they were representative of the (numerous and varied) groups responsible for health funding and research in the Member States.

For example, the list of organizations in annex 2.2 is very short: there are few professional societies, national research funders or regulators of medicines or devices.

Reported and not actual changes in activities: Most of the data provided to support the conclusions and recommendations were self-reported (attitudes, awareness or activity) or documentary analyses of changes in policy. There were few concrete examples of actual changes in activities or outputs consistent with the broad aims of the GSPA-PHI. No use was made of data sources that might have revealed progress, or otherwise, in areas covered by the GSPA-PHI (e.g. G-Finder reports). The data may indicate upstream changes, but no empiric, quantitative data were provided to demonstrate that the GSPA-PHI has made a meaningful (or any) systematic difference in any of the elements. In view of how long the GSPA-PHI has been in existence, it should have been possible to find data on the alignment of research funding and burden of disease (for element 1) and similar quantitative analyses for all elements. Without quantitative data demonstrating changes over time consistent with the recommendations of the GSPA-PHI, it is impossible to determine whether it has had an effect on health or research.

Co-occurrence, not causally related: As noted above, the evaluation acknowledged that activities that were aligned with elements of the GSPA-PHI might have been undertaken anyway. This is consistent with the general lack of awareness of the GSPA-PHI identified in the evaluation and applies to almost all the actions of various stakeholders, although WHO took some action directly as a result of the GSPA-PHI or in response to requests from the World Health Assembly in the context of follow-up of the GSPA-PHI or the recommendations of the CEWG.

Conclusions for which there is no evidence: Most of the conclusions are presented without supporting data or references. Numerous statements begin with the words “data show…” or “there is evidence that…”, but none are referenced. This undermines the credibility of the conclusions and may overestimate the impact of the GSPA-PHI. For example, on page 6 (under “key achievements”), it is claimed that the GSPA-PHI promoted health R&D in all income groups and improved access to knowledge and technology. That is a substantial claim which is not supported by data; moreover, it contradicts the point made elsewhere about the difficulty of attributing outcomes directly to the GSPA-PHI.

Limited specificity, feasibility and sustainability of the recommendations: Like the GSPA-PHI itself, the 32 recommendations are ambitious and unquantified. For example, the first recommendation states,

> Member States to promote upstream research in lower-middle-income and low-income countries with strengthened international cooperation and joint work between the public and private sector in areas that address their health needs, as well as at the international level and between high-income and lower-middle countries.

The other 31 recommendations for the eight elements are similarly vague and ambitious and would be impossible to implement or monitor in their present form. In that respect, the recommendations perpetuate one of the fundamental weaknesses of the GSPA-PHI; indeed, many of the recommendations restate or paraphrase the actions or sub-elements in the Plan. The recommendations are of a scale and scope that defy implementation.

No prioritization of recommendations: The recommendations are not prioritized according to their importance or feasibility but are presented as a flat, multi-faceted agenda. Given the scale and scope of the recommendations and the large resource implications for Member States, WHO and stakeholders, this is problematic and, once again, perpetuates weaknesses in the GSPA-PHI itself.

Unusable conceptual model for implementation of the GSPA-PHI by stakeholders: The conceptual model is informative but lacks the detail necessary to describe the obstacles to, and enablers of, GSPA-PHI implementation by stakeholders. This limits its use in preparing a plan for implementing the GSPA-PHI. The force field diagram presented is not sufficiently specific about who, when and

how elements should be implemented and, somewhat contrary to the theoretical basis of force fields, assumes a single, static introduction of the GSPA-PHI.

Data analysis and presentation: Many of the data components appear to be undefined and are therefore difficult to interpret and accept. For example, the units used in analysing data, the meanings of the bar graphs and the lack of uncertainty estimates appear to be unnecessary oversights.

Apparent lack of content expertise. The evaluation appears to reveal a lack of familiarity with the main subject matter of the GSPA-PHI. This may account for the lack of specificity in many of the comments and statements made. Moreover, there are several factual errors, which should not be present in such a report; for instance, on page 97 it is stated that the CEWG reported in 2015, when it actually reported in 2012.

5.4 Conclusion

Even allowing for the weaknesses identified above, two main conclusions can be reliably made.

- *Little awareness of the GSPA-PHI*. Stakeholders, and particularly organizations directly responsible for health research nationally appeared to be relatively unaware of the GSPA-PHI. Thus, not even the first step has been taken in implementation. Awareness appears to be better the more closely stakeholders are involved with WHO.
- *The scale and scope of the GSPA-PHI preclude its implementation*. An inescapable conclusion from the detailed report of the evaluation and its recommendations is that even partial implementation of the strategy would be more than challenging in favourable high-income settings and impossible in the low-income settings in greatest need. By covering multiple elements of the pathway from research, to practice, to policy, with the implicit aim of reaching all Member States, the GSPA-PHI may have become too unwieldy for effective implementation. To be effective, the GSPA-PHI would have to affect the work of research funders, researchers, regulators of medicines and health products, funders of medicines and health products and health care regulators and providers at national, state and local levels and in all Member States. This proposition is not realistic.

Chapter 6.

The way forward

6.1 Introduction

This chapter briefly reviews issues in implementation of the GSPA-PHI, lessons to be learnt and options for the way forward. Although there has been some progress in relation to both innovation and access, many of the problems that motivated formulation of the GSPA-PHI remain, and new challenges have emerged. While the pipeline of products in development contains some of particular relevance to developing countries, funding for their R&D has not increased sustainably since 2008. There has been some improvement in access – 19.5 million people accessed HIV treatment in 2016 and 4 million in 2008 (although the 19.5 million represent only just over 50% of the 36 million who still need treatment). However, the fundamental problems that the GSPA-PHI was designed to address remain and have become more serious. These include a lack of availability of essential medicines and inappropriate use, a lack of affordability of many new medicines, inadequate financing, a lack of new health products in areas of need, poor health delivery and supply chain infrastructure and inadequate regulatory frameworks and human resources, mainly but not exclusively in developing countries.

One of the main questions to be asked is whether the GSPA-PHI in its current form is effective for addressing these many challenges in innovation and access and for motivating governments and other stakeholders to take concrete steps to address them.

6.2 Review of the global strategy and plan of action on public health, innovation and intellectual property

The GSPA-PHI is unusual among global strategies sponsored by WHO in that it was the product of an intergovernmental working group, which negotiated the text line by line. Most global strategies of this nature are formulated by WHO or an advisory group after extensive consultations with Member States and external stakeholders, and the text is then approved by Member States in the World Health Assembly. There are many examples; a recent one is the global strategy and plan of action on ageing and health, which was approved by the World Health Assembly in 2016 *(198)*.

The unique method by which the GSPA-PHI was constructed accounts for some of the problems in its implementation, as discussed in Chapter 5, and particularly its ambitious scale and scope (25 sub-elements, 108 specific actions). In addition, the negotiated language often results in recommendations that are general and heavily qualified in ways that make progress difficult to assess and measure. This may partly explain why it has been difficult to monitor progress against the selected indicators effectively. Moreover, the GSPA-PHI lacks a coherent implementation strategy and plan and an efficient governance mechanism.

The lack of clarity on how different stakeholders should contribute to executing each action presents a clear challenge to implementation. Almost all the specific actions are addressed to governments and 49 to WHO. While there are mechanisms for holding WHO accountable for taking the lead in actions (the Executive Board and the World Health Assembly), there is no corresponding mechanism for governments, let alone the many stakeholders that are not assigned a leading role. This situation is similar to that for the SDGs, but the GSPA-PHI is not regularly monitored, with no regular reporting and poor public awareness. A relative lack of awareness of the GSPA-PHI among the government and nongovernment entities that were supposed to be active in its implementation was identified in the evaluation. Thus, the GSPA-PHI does not have the visibility of other global initiatives such as the MDGs and the SDGs. Lack of awareness of. or lack of motivation to implement the GSPA-PHI by the people and organizations that should be involved is a principal barrier to its implementation.

6.3 Recommendations

Our terms of reference were to "recommend a way forward, including details of what elements or actions should be added, enhanced or concluded in the next stage of implementation of the global strategy and plan of action on public health, innovation and intellectual property, until 2022". The aim of the GSPA-PHI is,

> to promote new thinking on innovation and access to medicines and, based on the recommendations of the report of the Commission on Intellectual Property Rights, Innovation and Public Health, provide a medium-term framework for securing an enhanced and sustainable basis for needs-driven essential health research and development relevant to diseases that disproportionately affect developing countries, proposing clear objectives and priorities for research and development, and estimating funding needs in this area.

We were asked to assess the continued relevance of the aim and objectives and of the eight elements of the GSPA-PHI. We consider that these are all still relevant in view of the persisting needs for R&D and access to health products, as summarized in previous chapters of this report, because of insufficient progress in implementing the GSPA-PHI since 2008. The main problem is lack of implementation. This suggests that our review can best add value by recommending priorities for action on each element to address current needs in R&D and access to medicines that are feasible, practical and, as far as possible, can be monitored, along with a governance mechanism for the GSPA-PHI, with a focus on implementation and monitoring. We therefore propose below a set of actions and indicators that meet these criteria, which, if achieved by 2022, would constitute real progress.

We prioritized 33 actions, rather than the 108 in the current GSPA-PHI. We sought to ensure feasibility, often by building on activities already being carried out by, or with the support of, WHO and other partners. We also took the view that the recommendations should be directed to the WHO Secretariat and/or Member States rather than the many stakeholders addressed by the GSPA-PHI. Although the activities of these stakeholders are integral to the success of the GSPA-PHI, we considered that it is for WHO and its Member States to encourage their appropriate involvement; furthermore, there is no mechanism for holding them directly to account. Finally, we emphasize the importance of establishing an implementation plan and a monitoring mechanism to track progress regularly.

Summary of proposed refinements to the GSPA-PHI

Refinement	GSPA-PHI	Review Panel proposal
More focused action	108 actions	33 actions
Prioritized action	No prioritization	17 high-priority actions
More specific action	31 overarching, often non-specific indicators, for 108 actions	33 measurable, action- and time-specific indicators
Specific responsibility for implementation	Broad assignment of responsibility for broadly defined actions	Responsibility for specific actions assigned to WHO and Member States
Specific responsibility for specific actions on monitoring	WHO and governments to establish monitoring systems, and report periodically to WHO on gaps and needs	WHO to draft implementation plan for publication in 2018, establish a monitoring mechanism to support implementation and publish reports at least annually. Member States to collect and report information to G-Finder

Our review also had to take into account developments in the world and in global health since 2008, as outlined in Chapters 2–4. In particular, for R&D and access to the health products required in developing countries, we had to take into account commitment to achieving the SDGs, including the implications of the movement towards universal health coverage. We also took into account relevant commitments in World Health Assembly resolutions to build human capacity for both R&D and health systems more generally for the achievement of the SDG health goals. Finally, we addressed the lack of effective monitoring and reporting systems under element 8 of the GSPA-PHI and the provision of adequate mechanisms of accountability.

We consider that WHO Member States should review our recommendations and incorporate them, with any amendments they wish to make, in a draft resolution for discussion by the World Health Assembly. Although not within our terms of reference, we consider that Member States should start thinking now about whether the GSPA-PHI should be extended in a more focused manner, in line with the recommendations of the present review, or succeeded by a new strategy in 2022. A necessary condition for success is adequate, sustainable funding by Member States, including for activities to be conducted by WHO.

We make the following proposals for actions between now and 2022. Those that we consider high priority are underlined. The dates proposed for achievement of the actions are indicative and may be amended in the proposed detailed implementation plan.

Recommendations

Prioritize research and development needs

- Member States to establish sustainable financing for the Global Observatory on Health Research and Development and the Expert Committee on Health Research and Development. (*Indicator*: Funding secured by 2019 to cover the projected budget up to 2022.)
- The WHO Secretariat to formulate a methodology for prioritizing research and development needs for types II and III diseases and the specific research and development needs of developing countries for type I diseases for use by the Expert Committee on Health Research and Development and by Member States, to enable them to identify, respectively, both global and national research and development priorities. *(Indicato*r: Methodology for prioritizing research and development needs prepared by 2018.)
- Report by the Expert Committee on Health Research and Development identifying health research and development priorities to address unmet medical needs based on evidence from the Global Observatory on Health Research and Development and on information provided by experts and relevant stakeholders. (*Indicator*: List of prioritized research and development needs for types II and III diseases established by 2019, with a final list including type I diseases established by 2020.)

Promote research and development

- Member States to support the WHO Secretariat in promoting transparency in, and understanding of, the costs of research and development. (*Indicator*: Reports on the costs of research and development for health products prepared in 2019 and 2021.)
- The WHO Secretariat to establish an information-sharing mechanism to promote collaboration and coordination in research and development linked to the Expert Committee on Health Research and Development and the Global Observatory on Health Research and Development. (*Indicator*: Establishment of an information-sharing mechanism to improve collaboration and coordination of resource allocation in accordance with research and development priorities by 2020.)
- Member States to promote programmes for collaboration with (and provision of support to) developing countries to strengthen clinical trial capacity and expert networks regionally and, where relevant, nationally. (*Indicator*: Report on mapping of programmes for strengthening clinical trial capacity and expert networks regionally and nationally by 2021.)
- Member States and the WHO Secretariat to encourage funders of research and development to ensure open access to all resulting publications immediately or, at the most, within six months of publication. (*Indicator*: Report by 2022 on new initiatives by funders of research and development to ensure that the resulting publications in peer-reviewed journals are open access.)

Build and improve research capacity

- The WHO Secretariat and Member States to develop and support collaboration programmes between internationally recognized centres for research and development and relevant institutions in developing countries to enable those countries to enhance their capacity across the research and development pipeline. (*Indicator*: Report on new collaboration programmes developed and supported by 2021.)

- The WHO Secretariat to continue providing support to strengthen the capacity of national and regional regulatory functions and systems, including for improving clinical trial regulatory review and oversight. (*Indicator*: Report on national and regional initiatives for strengthening clinical trial regulatory capacity in developing countries by 2019 and 2021.)
- The WHO Secretariat, in collaboration with Member States, to construct and promote the use of a database of relevant training programmes and materials for scientists and other experts involved in research and development from the public and private sectors in developing countries. (*Indicator*: Database of relevant training programmes and materials established and populated, and its use promoted by 2021.)
- Member States to promote the availability of training courses of certified quality, including online courses, for personnel involved in research and development. (*Indicator*: Monitoring the availability of certified quality training courses on research and development.)
- Member States, with the support of the WHO Secretariat, to develop strategies and strengthen their capacity for policy formulation, regulation, research methodology and ethics, and resource preservation in traditional medicine in line with the WHO traditional medicine strategy: 2014–2023. (*Indicator*: Report on national and regional programmes for developing strategies and strengthening capacity in research and development for traditional medicine by 2022.)

Promote transfer of technology

- The WHO Secretariat to identify mechanisms to increase health technology transfer in the context of the Technology Facilitation Mechanism established by the Sustainable Development Goals. (*Indicator*: Report on the identification of mechanisms to increase health technology transfer in the context of activities related to the Technology Facilitation Mechanism by 2020.)
- The WHO Secretariat to work with the secretariat of WTO to identify how Article 66(2) of the Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS Agreement) could be implemented more effectively in relation to health technology transfer in countries. (*Indicator*: Report on progress on health technology transfer related to implementation of Article 66(2) of the TRIPS Agreement by 2021.)
- The WHO Secretariat to identify new opportunities for collaboration with other United Nations organizations (e.g. UNIDO, UNCTAD) to promote technology transfer as part of local health technology production programmes in developing countries in line with country needs. (*Indicator*: Inter-organizational report on national technology transfer programmes developed and disseminated by 2022.)

Manage intellectual property to contribute to innovation and public health

- The WHO Secretariat, in collaboration with other international organizations working in intellectual property, to advocate for the development of national legislation to fully reflect the flexibilities provided in the TRIPS Agreement, including those recognized in the Doha Declaration on the TRIPS Agreement and Public Health and in Articles 27, 30 (including the research exception and “Bolar” provision), 31 and 31bis of the TRIPS Agreement. (*Indicator*: Inter-organizational report on national legislation and patenting guidelines that include the flexibilities provided in the TRIPS Agreement prepared by 2021.)
- The WHO Secretariat, in collaboration with partners, to promote the further development of databases of patents and non-confidential licensing agreements for health products and facilitate greater access to such databases. (*Indicator*: Monitor coverage and use of existing and new databases of patent and licence information.)

- Member States and other funders, with WHO Secretariat support, to strengthen the Medicines Patent Pool, which may include support for the expansion of its portfolio to cover other diseases or technologies for which the Medicines Patent Pool model can have the most impact. (*Indicator*: Number of diseases and/or technologies covered by the Medicines Patent Pool's portfolio and amount of funding committed by new donors by 2020.)
- Member States, when negotiating trade agreements, to take into account the impact on public health of adopting provisions that go beyond the requirements of the TRIPS Agreement. (*Indicator*: Assessment by 2022 of evidence that negotiators of new trade agreements have taken account of the public health impact of the adoption of such agreements.)

Improve delivery and access

- The WHO Secretariat to develop and share good practices on evidence-based selection and health technology assessment for health products for national use, and support bilateral and regional collaboration between countries. (*Indicator*: Good practices on evidence-based selection and health technology assessment developed and disseminated by 2019. Report on bilateral and regional collaboration programmes prepared by WHO by 2022.)
- The WHO Secretariat to provide guidance to Member States on promoting and monitoring transparency in medicine prices and on implementation of pricing and reimbursement policies. (*Indicator*: Guidance on promoting and monitoring transparency in medicine prices and on implementation of pricing and reimbursement policies developed and disseminated in countries by 2020.)
- The WHO Secretariat, in cooperation with Member States and other partners, to establish mechanisms to monitor patient out-of-pocket expenditure on health products. (*Indicator*: Monitoring patient out-of-pocket expenditure on health products.)
- The WHO Secretariat to continue to support Member States in strengthening national regulatory capacity, regional harmonization and other collaborative initiatives for improving access to new and existing quality-assured medicines and health products. (*Indicator*: Report on progress of national and regional regulatory capacity-building efforts in developing countries by 2021.)
- Member States and funders to support the WHO Prequalification of Medicines Programme to include newer essential health products, encompassing medicines, vaccines, diagnostics or biologicals. (*Indicator*: Number of newer health products included in the portfolio of the Prequalification of Medicines Programme by 2020 and 2022.)
- The WHO Secretariat to develop best practices and implement capacity-building programmes for more appropriate use of new and existing medicines and health products in national clinical practice. (*Indicator*: Best practices developed and capacity-building programmes implemented in countries by 2021.)
- The WHO Secretariat to promote best practices in countries and regional institutions to improve procurement and supply chain efficiency, including for joint procurement. (*Indicator*: Assessment of national and regional initiatives for promoting good practices to improve procurement and supply chain efficiency by 2022.)
- Member States to identify essential medicines that are at risk of being in short supply and mechanisms to avoid shortages, and disseminate related information accordingly. (*Indicator*: Lists of medicines at risk of being in short supply and information on mechanisms for preventing shortages made available and disseminated by 2020.)

Promote sustainable financing mechanisms

- Member States to commit to dedicating at least 0.01% of their gross domestic product to basic and applied research relevant to the health needs of developing countries. (*Indicator*: Percentage of gross domestic product dedicated to basic and applied research as reported by G-Finder by 2021.)
- Member States to commit to increasing domestic resource mobilization and supporting the Addis Tax Initiative in order to, inter alia, implement the health-related Sustainable Development Goals. (*Indicator*: Data from Member States on domestic resource mobilization gathered by 2021.)
- Member States to encourage the implementation of schemes that partially or wholly delink product prices from research and development costs, including actions recommended by the Consultative Expert Working Group on Research and Development: Financing and Coordination. (*Indicator*: New schemes to partially or wholly delink product prices from research and development costs developed, approved and implemented by 2022.)
- Member States, with the WHO Secretariat's support, to encourage an increase and diversification of funding for product development partnerships. (*Indicator*: Increased and diversified funding for product development partnerships and progress as reported by G-Finder by 2022.)

Establish a monitoring and accountability mechanism

- The WHO Secretariat to draw up a detailed implementation plan and establish a mechanism to support implementation and monitoring of the global strategy and plan of action. (*Indicator*: Implementation plan published and a mechanism for implementation and monitoring of the global strategy and plan of action established in 2018, and progress reports published at least once a year.)
- Member States to commit to providing information to G-Finder. (*Indicator*: Number of countries that have provided information to G-Finder.)

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Annex

Principles of the global strategy and plan of action on public health, innovation and intellectual property

- WHO's Constitution states that "the objective of WHO shall be the attainment by all peoples of the highest possible level of health". Accordingly, WHO shall play a strategic and central role in the relationship between public health and innovation and intellectual property within its mandates (including those contained in relevant Health Assembly resolutions), capacities and constitutional objectives, bearing in mind those of other relevant intergovernmental organizations. In this context, WHO, including its regional and, when appropriate, country offices, needs to strengthen its institutional competencies and relevant programmes in order to play its role in implementing this global strategy with its plan of action.
- The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition.
- The promotion of technological innovation and the transfer of technology should be pursued by all States and supported by intellectual property rights.
- Intellectual property rights do not and should not prevent Member States from taking measures to protect public health.
- International negotiations on issues related to intellectual property rights and health should be coherent in their approaches to the promotion of public health.
- The strengthening of the innovative capacity of developing countries is essential to respond to the needs of public health.
- Research and development of developed countries should better reflect the health needs of developing countries.
- The global strategy and the plan of action should promote the development of health products and medical devices needed by Member States, especially developing countries, that are:
  a) developed in an ethical manner,
  b) available in sufficient quantities,
  c) effective, safe and of good quality,
  d) affordable and accessible and
  e) used in a rational way.
- Intellectual property rights are an important incentive in the development of new health care products. However, this incentive alone does not meet the need for the development of new products to fight diseases where the potential paying market is small or uncertain.
- Several factors contribute to the price of health products and medical devices, and public policies should address these factors to increase their affordability and accessibility. Among others, competition and reduction or elimination of import tariffs on these products and devices can contribute to the reduction of prices. Countries should carefully monitor supply and distribution chains and procurement practices to minimize costs that could adversely influence the price of these products and devices.