EXECUTIVE BOARD **EB144/18**
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Medicines, vaccines and health products

Cancer medicines

Report by the Director-General

1. In 2017, the Seventieth World Health Assembly adopted resolution WHA70.12 on cancer prevention and control in the context of an integrated approach, in operative paragraph 2(9) of which it requested the Director-General to prepare a comprehensive technical report for consideration by the Executive Board at its 144th session that examines pricing approaches, including transparency, and their impact on availability and affordability of medicines for the prevention and treatment of cancer, including any evidence of the benefits or unintended negative consequences, as well as incentives for investment in research and development on cancer and innovation of these measures, as well as the relationship between inputs throughout the value chain and price-setting, financing gaps for research and development on cancer, and options that might enhance the affordability and accessibility of these medicines.

2. To assist with the preparation of the report, the Secretariat convened meetings with the Essential Medicine List Cancer Medicines Working Group and an informal advisory group on availability and affordability of cancer medicines, whose experts provided advice on the technical approach to assessing benefits of cancer medicines, the scope of the report, analytical feasibility and case studies, and suggested options that might improve the affordability and accessibility of cancer medicines.

3. The Secretariat also (a) reviewed empirical studies and "grey" literature; (b) conducted quantitative and qualitative analyses of data and information gathered from public sources; and (c) collated examples and case studies. The draft report was reviewed by the members of the informal advisory group.

4. The executive summary is presented in the Annex; the full report will be available in English on the WHO website.[1]

ACTION BY THE EXECUTIVE BOARD

5. The Executive Board is invited to note the report.

[1] http://www.who.int/medicines/areas/access/Improving-affordability-effectiveness-of-cancer-medicines/en/.

ANNEX

EXECUTIVE SUMMARY

Scope

1. This report examines pricing approaches adopted by the pharmaceutical industry and authorities responsible for the pricing of medicines, with a specific focus on medicines for the prevention and treatment of cancer. The report reviews pricing approaches applied throughout the "value chain" (i.e., activities required to bring medicines to patients, from research and development to service delivery), and at different time points of product life cycle from market launch to the entry of clinically substitutable medicines (that is, medicines with similar chemical structure and therapeutic effects, so-called "me too" medicines; and generic and biologically similar medicines).

2. This comprehensive technical report presents evidence relating to the impacts of pricing approaches (or lack thereof) on the price, availability and affordability of cancer medicines. It examines the possible relationship between pricing approaches and (a) research and development of cancer medicines, including incentives for investment in research and development on cancer and in innovation of these measures, as well as possible gaps in undertaking research and development (that is, a possible shortfall in funding or activities in certain areas of cancer research); (b) transparency in price and governance; and (c) benefits and unintended negative consequences that would deviate from the original policy intent. Options that might enhance the affordability and accessibility of cancer medicines are outlined in paragraphs 41 and 42 below.

Context

3. Cancer is one of the greatest global public health challenges. There are many types of cancer, with different causes, manifestations and prognoses. The global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths in 2018. Cancer has broad societal impacts beyond the negative effects it has on individual health outcomes, including productivity losses for cancer patients and their family caregivers.

4. Over the past decades, governments have worked with stakeholders to implement a spectrum of preventative and therapeutic interventions, from vaccination and screening programmes to surgical, pharmacological, radiological and social interventions for the treatment, rehabilitation and palliation of people with cancer. These collective efforts in diagnosis and treatment have resulted in great improvements in survival rates, which nonetheless continue to vary considerably by type of cancer and geographical region. For example, over 80% of children diagnosed with cancer in high-income countries will be cured of the disease, in contrast to rates as low as 10% among children diagnosed with cancer in low- and middle-income countries, which, despite having almost 80% of the burden as measured by disability-adjusted life years, are estimated to have a less than 5% share of global resources for combating cancer.

5. Data from multiple sources show that the rate of growth of expenditure on cancer medicines greatly exceeds the rate of growth of newly diagnosed cancer cases. Increased use of cancer medicines may be partly responsible for the growing expenditure. However, the growing expenditure may be primarily due to increases in medicine prices or a shift towards using higher-cost cancer medicines. In addition, the rate of growth of expenditure on cancer medicines exceeds the rate of growth of overall health care expenditure.

6. Existing approaches to managing the prices of cancer medicines have not resulted in outcomes that meet policy and economic objectives. Stakeholders continue to voice their concerns about the lack of adequate access to both new and off-patent essential cancer medicines, with high prices cited as a main contributory factor. Furthermore, overall prices of cancer medicines continue to rise, to the extent of impairing the capacity of health care systems to provide affordable, population-wide access to cancer medicines.

7. Access to cancer medicines is linked to systemic factors such as financial resources, insurance coverage, availability and skill set of the health workforce, health care infrastructure and physical access to health services. Thus, strategies to improve people's access to cancer medicines should be considered holistically across all surgical, pharmacological, radiological and social interventions for the prevention, treatment, rehabilitation and palliation of people with cancer. Such strategies should also be assessed with respect to the entire health care sector, so that the benefits of improving access to cancer medicines are not achieved at the expense of essential health care products and services for other disease areas.

Benefits and risks of newer cancer medicines

8. Pricing of cancer medicines is often discussed alongside a discussion of their benefits, particularly for newer cancer medicines. Cancer medicines that target a particular molecular alteration developed in past decades (targeted therapies) may represent advances in the treatment of cancer. Some targeted therapies have been shown to result in substantial improvements in health outcomes, such as overall survival and quality of life, and have transformed patient care for several cancer types. However, literature indicates that a considerable proportion of targeted therapies approved in the past 15 to 20 years have data only for improvement in surrogate endpoints, such as change in tumour size, without evidence of a benefit in terms of survival or quality of life. For some medicines that have been found to have an impact on survival, the size of the benefit may still be small; the average benefit is 3 months, which may be considered marginal by clinical experts. Furthermore, some medicines may present higher risk of toxicities to patients, with evidence of high rates of deaths related to treatment (toxic deaths) and high chances of patients discontinuing treatment due to intolerance. In assessing the benefits of cancer medicines, it is important to conduct a comprehensive evaluation of all evidence by combining results across clinical trials and appraising the consistency of evidence in its totality. It is also important to identify the potential limitations of evidence obtained in terms of its generalizability to different health care systems.

Industry approaches to price-setting

9. The literature describes four broad determinants of medicine prices from the industry perspective: (a) costs of research and development; (b) costs of production and commercialization; (c) the "value" of medicine; and (d) sufficient returns on research and development.

10. Estimates of research and development costs, including for cancer medicines, are highly variable and not transparent. Reported estimates, after adjustments for the probability of trial failure and opportunity costs, range between US$ 100–150 million and US$ 4–6 billion, but the most commonly accepted estimates are between US$ 200 million and US$ 2.9 billion.

11. "Value-based pricing" has been proposed as a method of pricing new medicines. However, there are many uncertainties associated with estimating value, as a result of different technical approaches to assessment, incomplete evidence, comparison with inefficient practices, and different perceptions of value. This method may lead to unaffordable prices for cancer medicines.

12. To examine returns on research and development investments, an analysis was undertaken to examine the sales incomes from cancer medicines approved by the United States Food and Drug Administration from 1989 to 2017 for the originator companies. For the 99 medicines included in the analysis, the average income return by end-2017 was found to be US$ 14.50 (range: US$ 3.30 to US $55.10) for every US$ 1 of research and development spending, after adjustments for the probability of trial failure and opportunity costs; 33 of those medicines had already qualified as "blockbuster drugs" by having an average annual sales income exceeding US$ 1 billion. Many medicines, particularly biologics, continued to generate high sales incomes for the originator companies after expiry of patents and the end of exclusive marketing rights.

13. Overall, the analysis suggests that the costs of research and development and production may bear little or no relationship to how pharmaceutical companies set prices of cancer medicines. Pharmaceutical companies set prices according to their commercial goals, with a focus on extracting the maximum amount that a buyer is willing to pay for a medicine. This pricing approach often makes cancer medicines unaffordable, preventing the full benefit of the medicines from being realized.

Payer approaches to price-setting

14. Authorities responsible for the pricing of medicines have adopted a range of approaches to set medicine prices, including cancer medicines, such as cost-based pricing, value-based pricing, reference pricing, and pricing through tendering and negotiation. Some authorities have also set a maximum "ceiling" price, while others have agreed to arrangements with manufacturers to enable access to cancer medicines subject to specified conditions, such as discounts or rebates based on volume of sales or payment according to health outcomes. These agreements are known as "managed entry agreements" or "risk-share agreements". The conditions of such arrangements are often agreed on confidential terms between manufacturer and purchaser.

15. Authorities in some countries have routinely monitored medicine prices, with a view to controlling prices throughout the supply chain and at various time points throughout the product life cycle. These strategies include regulating mark-up amounts, reassessing prices when there is a change in market conditions, such as entry of generic and biosimilar products, or when the indications for an individual medicine change.

16. Authorities in some countries have also used other strategies to achieve greater system efficiencies and improve access to cancer medicines that may have an indirect effect on prices, including (a) requiring clinicians to obtain approval from the payer before prescribing or dispensing a select set of high-cost and highly-specialized cancer medicines; (b) implementing policies to encourage prescribing and substitution of cancer medicines with generic or biologically similar products to increase competition; (c) reduction or exemption of taxes on medicines; and (d) implementing pooled procurement of medicines by combining financial and non-financial resources across various purchasing authorities in order to create greater purchasing power through economies of scale and better negotiation position.

Relationship between inputs throughout the "value chain" and price-setting

17. Overall, there are gaps in data and information regarding the activities and costs required to bring medicines to patients, throughout the value chain from research and development to service delivery. Moreover, the precise relationship between "value chain" inputs and price-setting is not known in many countries, particularly in low- and middle-income countries.

Impacts on price

18. Prices and costs of many cancer medicines are high, in recent decades often reaching tens of thousands of US dollars per patient per year, while comparative analyses show that they exceed the prices and costs of medicines used for treating other diseases.

19. Current pricing policies (or the lack thereof) have led to considerable variability in the prices of cancer medicines within a country and across regions. Evidence from published literature shows that the observed price variability does not seem commensurate with the demand or a given country's purchasing power, while existing procurement practices in some countries may not be very efficient. When prices of cancer medicines are higher than a country's ability to pay, this may impair coverage of essential cancer medicines, causing delay in patient access to medicines and limiting the system's ability to achieve the best possible patient health outcomes. Finally, regional differences in medicine prices within a country may cause inequitable access.

20. Evidence suggests that a lack of effective and consistent policies for managing medicine prices across the supply chain (i.e., taxes and mark-up amounts) over time can result in uncontrolled and highly dispersed prices for the same medicine. Furthermore, inconsistent pricing policies across service delivery settings within a health care system (such as hospitals and outpatient facilities) can result in inefficient cost-shifting activities and inequitable access for patients.

21. Comparative analyses indicate that more pricing regulations may contribute to lower medicine prices and costs. Yet even in countries that have implemented a range of policy measures to manage medicine prices, the prices of newer cancer medicines have continued to grow substantially in recent decades. Thus, more measures may be needed to realign the prices of cancer medicines and expand access to cancer medicines by treating higher patient numbers at lower average costs, thus ensuring the long-term financial sustainability of health care systems and industries.

22. Policies that facilitate price competition among pharmaceutical companies for clinically substitutable medicines have generally led to lower prices of generic brands compared to their originator counterparts, yielding expenditure savings. However, the extent to which pricing policies can enhance competition and reduce medicine prices is dependent on a range of factors, such as existing price and non-price policies; the number of competing companies and the size of products and markets; regulatory requirements and processes for generic and biosimilar medicines; and enforcement of robust competition policies to prevent companies from engaging in behaviours that may impair competition. Documented examples of anti-competitive behaviours by companies include introduction of "pseudo-generics", tacit or actual collusion, "product hopping" (switching a patented medicine to a modestly reformulated product that offers little or no therapeutic advantages in order to preserve market exclusivity) and wasteful non-value-added activities, such as lobbying or filing patent clusters to delay generic/biosimilar entry.

Impacts on availability

23. Two large surveys examined the availability of medicines for solid tumours in the national formularies of 49 European countries in 2014 and 63 countries outside Europe in 2016. Data showed that countries with lower national income had lower availability of cancer medicines, or availability only with higher out-of-pocket patient payments, especially for higher-cost medicines, including targeted therapies. One survey found that 32.0% and 57.7% of essential medicine list cancer medicines were available in lower-middle-income countries and low-income countries, respectively, only if patients were willing to incur their full costs.

24. Case studies from several countries show that the judicious selection of cancer medicines and the rational application of access requirements with consideration of the specific health-system context can deliver better health outcomes to cancer patients for the available financial resources. A policy of trying to fund the same number of cancer medicines as are available in other countries will not result in substantive health improvements, but will result in significantly higher costs. Countries should instead consider their specific health care context, including factors such as population need and available funds.

25. However, there is evidence that in some countries, cost-containment measures undertaken due to the high costs of cancer medicines, irrespective of population needs, have resulted in reduced, delayed and even cancelled treatment, which may have adverse impacts on patient health outcomes. While differences in system capacities and population needs must be recognized, policies for controlling costs to ensure system sustainability must be balanced with the primary objective of facilitating timely patient access to medicines.

Impacts on affordability

26. A modelling study shows that universal coverage of cancer medicines alone, at 2018 prices, would greatly exceed a generously assumed budget of 5% of the total health care expenditure: standard treatment regimens for a selected set of cancers would cost much more than the estimated annual per-patient "budget" of US$ 800 (low-income countries) to US$ 40 600 (high-income countries).

27. In the absence of insurance coverage, cancer treatment is unaffordable for many patients. A course of standard treatment for early stage HER2 positive breast cancer (doxorubicin, cyclophosphamide, docetaxel, trastuzumab) would cost about 10 years of average annual wages in India and South Africa and 1.7 years in the United States of America. The costs associated with other medical care and interventions (such as surgical interventions and radiotherapy) and supportive care (such as anti-emetics and haematopoietic growth factors) would make overall care even more unaffordable. Even with insurance coverage, patients living with cancer in many countries have reported financial stress, to the extent that they may lower the treatment dose, partially fill prescriptions or even forego treatment altogether.

Impacts on research and development

28. In 2017, there were almost twice as many registered clinical trials on cancer medicines as in the next four highest therapeutic categories combined. Leading experts have noted significant inefficiencies of cancer drug trials due to duplication of research efforts and the pursuit of marginal therapeutic indications with non-clinically significant health outcomes. Some failed investments could have been prevented given the lack of compelling evidence of efficacy in humans prior to embarking on major clinical trial programmes.

29. While acknowledging the tremendous challenges in finding effective and safe cancer medicines, the trial redundancy (that is, duplication of trials that may be unnecessary) of cancer medicines suggests that excessive financial returns combined with market dominance have encouraged companies to engage in excessive risk-taking in research and development by investigating cancer medicines despite the lower probability of success. Simultaneously, companies have adopted a "de-risking" strategy by pursuing marginal indications with the expectation that the market would continue to bear high prices in the name of so-called "innovation". In the long term, such distortion of investment and corporate behaviour will stifle genuine innovation.

30. Concerns that lower cancer medicine prices might impair future research and development seem misplaced because evidence suggests that (a) prices of cancer medicines bear little or no relationship with research and development costs; (b) financial returns of cancer medicines are high; (c) potential impact on revenue due to lower prices could be offset by higher volume, especially when the marginal cost of production is low; and (d) governments and the non-profit-making sector have made substantial contributions to the research and development of medicines through direct funding and other incentives.

31. The public sector has made a wide range of contributions to the research and development of medicines generally, including cancer medicines, ranging from providing direct funding of basic science research and clinical trials to building physical research infrastructure, supporting the operation of institutions such as cancer registries, building medical research workforces through education programmes and incentivizing research and development through tax credits or reductions. Such public-sector investment has often led directly to the discovery and development of cancer medicines such as abiraterone, temozolomide and enzalutamide.

32. Given this consideration, some stakeholders have questioned whether pharmaceutical companies can legitimately claim to recover the full costs of research and development by setting high prices for medicines. They see a need to clarify whether the public has been "paying twice", or should be paying twice, for medicines developed with at least partial support from public resources. It is also important to clarify the relationship between the government, industry and universities when pursuing joint research ventures.

33. Determining research priorities and gaps requires both technical assessments and value judgments. Studies have suggested that research on haematological and breast cancers may be overfunded, while research on cancers of the liver, thyroid, lung, oesophagus, stomach, bladder and pancreas may be underfunded; these studies have assumed that the allocation of research funding for each type of cancer should be in proportion to their respective disease burden. However, as society may have a higher preference to help children and young mothers, the prioritization of research for haematological and breast cancers may be considered justified.

Impacts on price transparency

34. The use of discounts and rebates may signal competition in the market and is often considered a legitimate competitive practice if applied legally. However, confidential agreements on rebates and discounts have obstructed market transparency, including information about the level of price competition.

35. Growing differences in list prices and net transaction prices of medicines (i.e. after discount and rebates) may mask actual increases in medicine price. Pharmaceutical companies may also be motivated to keep list prices high to impair the effectiveness of external reference pricing.

36. Non-transparent medicine prices may conflict with the principles of good governance and confidential agreements may compromise clear lines of accountability. A lack of price and process transparency may even lead to corruption, especially in health care systems with weak overall governance.

37. Theoretical arguments on whether greater price transparency would lead to higher or lower medicine prices are inconclusive. There is a lack of evidence of the effectiveness of confidential agreements in lowering prices and improving access. On the other hand, there is limited context-specific evidence that improving price transparency has led to better price and expenditure outcomes. Nonetheless, improving price transparency should be encouraged on the grounds of good governance.

Unintended negative consequences

38. Current research and development incentives, regulatory flexibility and pricing practices for medicines to treat rare diseases (orphan drugs) may have led pharmaceutical companies to pursue an indication for rare cancer in the first instance and then expand the indication to other more common cancers, with a view to gaining faster market entry at high prices.

39. There have been documented cases of disruption in the supply of cancer medicines in recent years. Causes of medicine shortages are complex and involve both supply and demand factors. Low market attractiveness due to low prices and small market sizes are possible contributing factors as well. However, data from regulatory reporting indicate that shortages of cancer medicines are probably due to problems related to meeting the quality standards for injections, rather than to lack of financial incentives to ensure the ongoing supply of lower-priced medicines. Overall, existing data on medicine shortages are not robust. Until more compelling evidence is presented, payers should not be deterred from seeking lower prices for fear of causing shortages. This will minimize the incentive for suppliers to prioritize higher-priced and more profitable medicines over lower-priced medicines.

40. There are some documented examples of inefficient, unethical and even illegal activities induced by the high prices or profitability of cancer medicines, including the emergence of substandard or falsified cancer medicines, practices prohibited by antitrust laws, deceptive marketing and activities for off-label prescribing.

OPTIONS THAT MIGHT ENHANCE AFFORDABILITY AND ACCESSIBILITY

41. A set of options that might enhance the affordability and accessibility of cancer medicines have been identified through a review of policy and evidence and consultations with experts, broadly pertaining to: (a) strengthening pricing policies at the national and regional levels; (b) improving the efficiency of expenditure on cancer medicines; (c) improving the transparency of pricing approaches and prices of cancer medicines; (d) promoting cross-sector and cross-border collaboration for information-sharing, regulation and procurement; (e) managing factors that would influence the demand for cancer medicines; and (f) realignment of incentives for research and development.

42. The options and proposed time frame are summarized in the following table.

Table. Options that might enhance affordability and accessibility of cancer medicines, including time frame

Option that might enhance affordability and accessibility of cancer medicines.	Level of action required				Time frame for action[a]			Proposed actions taken by:				
	Local	Regional	National	Inter-national	Short	Medium	Long	Government^	Payer^	Industry	Health care professional	Patients
(a) Strengthening pricing policies												
(a.1) Improving the consistency of policies across health and other sectors	○	●	●		▭	▭		✱	✶	✶		
(a.2) Designing differential pricing sensitive to health systems' ability to pay			○	●		▭	▭	✶	✱			
(a.3) Enhancing health system ability to review and adjust prices, and to withdraw funding for superseded or less cost-effective medicines if required	○	●	●		▭	▭			✱	✶		
(a.4) Enforcing price caps for cancer medicines, with or without progressive reduction of prices over time		●	●		▭	▭			✱			
(a.5) Creating competition among substitutable cancer medicines		○	●		▭	▭		✶	✱	✶	✶	✶
(b) Improving efficiency												
(b.1) Prioritizing the selection of medicines with high(er) clinical value		●	●	○	▭	▭		✶	✱		✱	
(b.2) Considering the costs of model of care as part of the pricing approach		●	●		▭	▭			✱			
(b.3) Considering managed entry agreements for expenditure control only in specific cases			●		▭			✶	✱			
(b.4) Avoiding the use or establishment of fund earmarked for the provision of cancer medicines			●		▭			✱	✶			

Option that might enhance affordability and accessibility of cancer medicines.	Level of action required				Time frame for action[a]			Proposed actions taken by:				
	Local	Regional	National	Inter-national	Short	Medium	Long	Government^	Payer^	Industry	Health care professional	Patients
(c) Improving transparency												
(c.1) Disclosing the net transaction prices of cancer medicines to relevant stakeholders			●	○	▭			✶	✶	✱		
(c.2) Disclosing and controlling prices along the supply chain	○	●	●		▭			✱	✱	✶	✱	
(c.3) Reporting the costs of research and development and production, including public sources of funding			○	●		▭		✶		✱		
(c.4) Communicating pricing and reimbursement decisions to the public, when appropriate		○	●		▭			✶	✱			
(d) Promoting cross-sector and cross-border collaboration												
(d.1) Sharing information on medicine prices and technical assessments			●	○	▭			✶	✱			
(d.2) Harmonizing regulatory requirements for biosimilar medicines to ensure safety and quality and to promote competition			●	○		▭		✱		✶		
(d.3) Streamlining cross-border regulatory requirements and supply management of medicines in shortage			●	○		▭		✱		✶		
(d.4) Pooling subnational, national and regional resources for joint negotiation and procurement		●	●			▭		✶	✱	✶	✶	
(d.5) Using voluntary license agreements where possible and applying WTO/TRIPS flexibilities for patented medicines, where appropriate			●					✱				

Option that might enhance affordability and accessibility of cancer medicines.	Level of action required				Time frame for action[a]			Proposed actions taken by:				
	Local	Regional	National	Inter-national	Short	Medium	Long	Government^	Payer^	Industry	Health care professional	Patients
(e) Managing demand-side factors												
(e.1) Removing financial/non-financial incentives for prescribing cancer medicines of limited clinical value	●	●	●		▭				✱	✱	✱	
(e.2) Restricting promotional activities of cancer medicines to clinicians and the public			●		▭			✱		✱	✶	
(e.3) Correcting any misperception of inferior quality of generic or biosimilar medicines		○	●		▭			✱	✶	✶	✱	✶
(e.4) Implementing regulatory measures upon identification of substandard and falsified medicines	●	●	●	●	▭			✱		✱	✱	
(f) Realigning incentives for research and development												
(f.1) Incentivizing research for cancers that affect smaller populations			●	●		▭		✱		✱	✱	
(f.2) Focusing on health service research to improve system efficiencies, rational use of medicines and packages of care		●	●		▭			✱			✱	✶

Key: WTO/TRIPS: World Trade Organization Trade-Related Aspects of Intellectual Property Rights.

[a] Short term: within 1 year; medium term: 1–3 years; long term: more than 3 years.

^ Government and payer may be the same.

● Primary level of action.

○ Complementary level of action.

✱ Primary actor.

✶ Complementary actors.