Pharmaceutical Policies in Cyprus: A Review of the Current System and Future Options

Panos Kanavos & Olivier Wouters
LSE Health, London School of Economics

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Abbreviations

ATC	Anatomical Therapeutic Chemical Classification System
DRG	Diagnosis Related Group
EFPIA	European Federation of Pharmaceutical Industries and Associations
EPR	External Price Referencing
EU	European Union
GDP	Gross Domestic Product
GeSY	Generalised Health Insurance Scheme
HIO	Health Insurance Organisation
HTA	Health Technology Assessment
INN	International Non-proprietary Name
IRP	Internal Reference Pricing
KEFEA	Cyprus Association of Research and Development Pharmaceutical Companies
MEA	Managed Entry Agreement
MoH	Ministry of Health
NICE	National Institute for Health and Care Excellence (UK)
OECD	Organisation of Economic Co-operation and Development
OTC	Over-The-Counter drug
POM	Prescription-Only-Medicine
PPP	Purchasing Power Parity
R&D	Research and Development
RSA	Risk-Sharing Agreement
TLV	Dental and Pharmaceutical Benefits Agency (Sweden)

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Executive summary

The pharmaceutical market in Cyprus is characterised by several country- and system-specific peculiarities and challenges, including:

- Small market size;
- The system of external price referencing (ERP) does not enable the country to capitalise on transaction prices in reference countries;
- The absence of a health insurance scheme and the resulting absence of a suitable reimbursement system does not allow the country to exercise any form of market power; this may lead to inequities in access and expose citizens to undue financial and health risks;
- There are no mechanisms in place to monitor and control the prescribing behaviour of physicians; coupled with brand awareness, this likely encourages the over-prescribing of expensive, on-patent products;
- There do not appear to be any limits on promotional activities by manufacturers and distributors or any self-regulating practices (such as a code of practice), potentially incentivising providers to induce demand;
- The pharmacy remuneration structure and the absence of generic substitution favour the dispensing of expensive products;
- For patients, there is little cost-sharing in the public sector, whereas drug costs are borne out-of-pocket in the private sector.

A World Health Organization (WHO) mission to study the current system of pharmaceutical pricing and coverage decisions resulted in a series of recommendations. Chronologically, these have been divided into three categories: first, interventions for the short-term to refine the way the current system works, aiming to increase its efficiency and economise on resources; second, interventions aiming to address gaps in the organisation and delivery of health and pharmaceutical services in anticipation of the introduction of a general health insurance scheme (GeSY); and, third, interventions aiming to ensure the sustainability of health and pharmaceutical care provision following GeSY implementation.

1. Recommendations for the short-term

A number of recommendations have been made for the short-term.

Recommendation 1: Watchful waiting for the tender (open invitation) market in the public sector. For this segment of the market, the Ministry of Health (MoH) should continue to implement the current tender system, which is state of the art and has delivered significant benefits over time. Further rationing of expenditure in the public system could only be achieved by examining how volumes are determined, or by influencing prescribing habits; demand-side interventions, however, are difficult to implement in the short-term in the current system.

Recommendation 2: Introduce risk-sharing agreements in the negotiation process of the public sector and respect the confidentiality of these agreements. Cyprus should leverage the existing legal framework to enable the competent authorities to negotiate with manufacturers and agree on prices on the basis of risk-sharing agreements. These agreements will be confidential in nature and will only be subject to statutory disclosures to government bodies for oversight purposes. As the

current legal framework does not allow for direct and confidential negotiation with manufacturers, it is recommended that such a framework be put together as a matter of priority.

Recommendation 3: This recommendation is split into four potential options for the MoH. We only propose that one of the following is adopted by the MoH (listed in order of preference, from most to least preferred).

- **Recommendation 3a: Re-calibration of prices derived through the current EPR reference basket by means of a wealth adjustment based on GDP differences.** The MoH should introduce a wealth adjustment to the prices derived from external price referencing; the wealth adjustment should be calculated as a function of GDP differences between Cyprus and the current basket of countries in the EPR scheme. Based on the decline in GDP per capita in Cyprus between 2009 and 2012, the level of correction would be 8.5%. If it is implemented in 2014, it will have an immediate impact on pharmacy retail prices in the private sector and, therefore, lessen out-of-pocket expenses for patients. Products priced less than €10 should be excluded from the practice. The public sector will only benefit from this wealth correction if it results in a starting point for the price negotiation of new tender contracts that is lower. The government will need to review the wealth adjustment annually and adjust the prices upwards or downwards accordingly.
- **Recommendation 3b: Implementation of an across-the-board price cut.** Implement a modest-to-moderate across-the-board price cut of 8.0-8.5%. However, it is important to ensure this will not have a spill-over effect in other countries that reference the Cypriot prices, which could jeopardise availability of these products in Cyprus.
- **Recommendation 3c: An across-the-board price reduction for off-patent originator drugs.** It is proposed that the MoH implements a price reduction between 20-30% to all off-patent originator brands. Generic versions of the off-patent originator brands should continue to be priced at 80% of the originator prices. A price decline in the above range will ensure savings to private sector patients and is unlikely to jeopardise supply to the public sector.
- **Recommendation 3d: Change the basket of countries for the calculation of the reference price.** The MoH should consider switching from the average price in the basket to the median or lowest price. Alternatively, the MoH could alter the composition of the basket, for example by considering drug prices in two low-price countries and one medium-price country. However, a price decline of over 8-10% may have adverse consequences for both the private and the public sectors in terms of availability, and therefore needs to be studied carefully before being implemented. Re-calibration of the EPR system can have long-term effects.

Recommendation 4: Introduction of annual price revisions. Price revisions/re-pricing should take place annually for all products on the market. This will allow the competent authorities to capitalise sooner on price revisions taking place in the reference countries.

Recommendation 5: Implementation of a one-off rebate on 2013 sales. The MoH should implement a one-off rebate in 2014 based on 2013 sales to the public sector. The rebate will be determined according to individual company market shares on a sliding scale. The average reduction would be in the region of 4-5%.

Recommendation 6: Legislation and limits on pharmaceutical advertising. It is recommended that the MoH introduces legislation establishing limits on all forms of pharmaceutical advertising by manufacturers and their representatives. The MoH should also ask manufacturers, their representatives, and medical professionals to put together appropriate codes of practice. Consequently, the MoH should attempt to fill the gap in the provision of information on pharmaceutical products to stakeholders.

Recommendation 7: Re-shape the pricing committee. The main goal of the pricing committee is to validate the results of the pricing formula and recommend products in question to the Minister of Health based on scientific and pricing information. The pricing committee membership should only include institutional stakeholders (medicines regulatory body and MoH) and scientific personnel. Once a system of reimbursement has been introduced, additional stakeholders (e.g. patients and industry) can participate.

Recommendation 8: Prescribing guidance in the public sector. For public-sector medicines, the government should pilot prescribing guidance in a small number of disease areas/conditions to encourage rational use; this should improve the quality of care and optimise spending. This could be done for a number of high cost conditions (e.g. hypertension, dyslipidaemia, and osteoporosis). This will enable the authorities to place individual drugs in the context of the disease and its treatment, as well as outline treatment options and their sequence and duration.

Recommendation 9: Tendering (open invitation) at therapeutic class level. It is recommended that for medicines that can be grouped into inter-changeable therapeutic clusters, tenders at therapeutic class level (e.g. across all statins or ACE inhibitors) be conducted. This could take place as a pilot and contracts could be awarded to the two or three lowest bids across the therapeutic class. The legislative implications first need to be explored before proceeding in case the current framework only allows for the lowest price to be the winner of the contract.

Recommendation 10: An information campaign to improve the perception of generic medicines. Improving the perception of generic medicines is essential as patients are currently sceptical about their value. The MoH could undertake an information campaign on the value and quality of generic medicines and their inter-changeability (bio-equivalence) to brands. This should deliver benefits over the longer term.

Recommendation 11: Re-visit the upper ceiling on pharmacy remuneration with a view to rationalise it downwards. It is recommended to reduce the maximum retail remuneration ceiling in line with levels currently prevailing in the rest of the EU. Overall, it may be necessary to re-visit the overall remuneration structure of retail pharmacy with the addition of regressive mark-ups at appropriate price ranges and, eventually a disconnect of pharmacy income from medicines' pricing.

2. Recommendations for the medium-term and in anticipation of GeSY implementation

The list below outlines a number of essential actions that need to be completed before the implementation of GeSY to ensure that (a) the legislative/institutional framework is up-to-date, (b) the competent authorities acquire time-sensitive knowledge of how the

country is likely to operate in an environment of health insurance and (c) the competent authorities identify and address some of the gaps and teething problems that such a system will have prior to its rollout to the entire population. These actions can be part of a 3-4 year work programme. It would not be wise to implement GeSY before these take place.

- Re-calibrate the system of pricing and maintain its independence relative to the system of reimbursement; re-define the role and membership of the pricing committee and undertake all necessary legislative changes. Define management roles and implement price revisions annually.
- Establish a national positive list or formulary by fusing the treatment options currently available in the public and private sector.
- Establish a reimbursement committee and all the processes around it (e.g. headcount, membership, transitional arrangements, etc), including a secretariat that is in charge of the background work related to the inclusion of new medicines on the positive list (i.e. formulary).
- Establish the criteria for admission of new drugs into the positive list, as well as criteria for de-listing. Establish a framework for over-the-counter medicines and the switch of compounds from prescription-only to over-the-counter medicines.
- Decide on the precise role of economic evaluation in the decision-making process and how to operationalise such a system (including capacity-building).
- Decide on the tools required to enable the Competent Authorities to negotiate successfully with manufacturers over new and expensive therapies (e.g. outcomes-based risk sharing, price volume agreements, etc); decide how to operationalise such negotiations and what capacity-building activities are needed.
- Introduce internal price referencing, which will encompass both molecular and therapeutic price referencing; define the therapeutic classes for which the latter can be implemented; simulate the impact on reimbursement across a range of therapeutic classes under conditions of health insurance for the entire market.
- Define the scope of tendering; identify likely targets for tendering and simulate the effect of tendering under conditions of a unified health insurance market across a number of products (e.g. on-patent, off-patent branded, and generic).
- Define the role of and scope for other reimbursement tools, such as portfolio management, and quantify their likely impact.
- Pilot the arrangements around primary health care (gate keeping), physician remuneration, and any incentives to improve quality of care prior to introduction of health insurance.
- Establish an electronic prescribing (e-Rx) system, which will require hardware, software, and pilot testing. If procured through open processes, as per EU directives, the time commitment can be significant. Once in place, it needs to be guaranteed it runs effectively by piloting it in one or two areas. As the process is onerous and subject to EU procurement rules, it may be wise to attempt to by-pass some of these restrictions by incorporating this task into the Memorandum of Understanding (MoU) targets as soon as possible.

- Conduct a pilot for the preparation of prescribing guidance for the ten most costly diagnoses/conditions in Cyprus.
- Link prescribing guidance to the e-Rx system and ensure that the system operates well.
- Pilot the implementation of e-Rx with prescribing guidance to determine physician compliance and expected savings.
- Simulations on cost of prescribing under the new conditions for the ten most expensive diagnoses/conditions at ATC-3 level under current circumstances; also simulate the cost effect when prescribing guidance has been produced and it is linked to the e-Rx system.
- A detailed and comprehensive study on pharmacy remuneration given that they will serve the entire market after health insurance implementation. This should be based on a comprehensive and representative sample of the public and private sectors.
- Identify a suitable cost-sharing policy, including exemption criteria and type of cost-sharing that will not carry a disproportionate financial burden for patients and administrative burden for health insurance. Link cost-sharing to the positive list.
- New legislation or amendments to existing legislation will need to be produced for many of the above areas once the evidence has been produced and discussions have taken place between the relevant stakeholders. Draft legislation can be bundled into coherent groups each addressing a subject area. It is envisaged that amendments to existing laws or new legislation will need to be produced as follows:
    - Amendments to the Law on Human medicines (Quality Assurance, Procurement, Pricing)
    - Amendments to the Law on Pharmaceuticals and Poisons
    - Amendments to the Law on Psychotropic and Narcotic Substances
    - Amendments to the Law on National Health System
    - Establish legal framework to enable confidential negotiations with manufacturers
    - Establish legal framework for the reimbursement of pharmaceutical products, the establishment of a reimbursement committee, the positive list, the roles remuneration and responsibilities of prescribers and pharmacists, and the co-payments by patients
    - Establish legal framework for INN prescribing and generic substitution
    - Establish legal framework for the contractual agreements between the medical profession and health insurance/the government.
- The roadmap will also include allocation of responsibilities and tasks among competent authorities to leverage the expertise developed to date.

3. Recommendations for the long-term

On the supply-side, the most needed change is the move to a system of reimbursement. It will be important for the HIO and Department of Pharmaceutical Services (MoH) to establish the parameters of a reimbursement system and the levels of coverage, for example based on therapeutic indication. This should also include drug evaluation criteria, most likely under the auspices of a newly-formed reimbursement committee. The terms of reference and the criteria for admission into reimbursement will also need to be established. Having a reimbursement system with clear and transparent rules, whilst at the same time enabling competent authorities to negotiate reimbursement rates for a number of niche products, is a challenge that needs to be addressed by focusing on increasing capacity, improving competences, and mastering tools and techniques related to clinical benefit assessment, cost-effectiveness, risk sharing, and internal price referencing, among other factors.

On the demand-side, most of the relevant changes should have been implemented in the short- and medium-term. It will be important to continue to enforce mandatory generic substitution and INN prescribing, as previously explained (assuming these have been implemented in the run-up to health insurance introduction). An electronic prescribing system – perhaps the single most important demand-side policy intervention - linked to professional prescribing guidance should enable prescribing and drug use to be monitored in real time. It would also enable competent authorities to introduce prior authorisation principles for drugs that are particularly costly. An important demand-side change under a national health insurance scheme will be the introduction of cost sharing for some drug classes to divide the cost burden between the health care system and patients. An appropriate cost-sharing policy will need to be implemented, including exemptions and cost-sharing rates. Exemptions should be based on socioeconomic conditions (e.g. income, age, etc.) and also include other safeguards to protect vulnerable populations. As previously mentioned, the internal reference pricing system will result in patients paying the difference between the reference price and a higher drug price if the patient elects to not purchase the lowest-priced drug. The government can also consider alternative cost sharing arrangements, including coinsurance, deductibles, and co-payments. Finally, the Cypriot competent authorities should review the provision of information to patients, including the provision of information on generic medicines.

1. Background and terms of reference

The Republic of Cyprus is a member state of the European Union (EU) with a population of 838,897 (2011 census). In 2012, the gross national income per capita in the country was PPP$29,840 and the life expectancy at birth for males and females was about 79 and 84 years, respectively. Cypriots enjoy levels of health that are comparable to other member states of the Organisation of Economic Co-operation and Development (OECD) (Theodorou *et al* 2012). In 2011, the total expenditure on health as a percentage of gross domestic product was 7.4%, which is lower than the OECD average. The health system consists of a public and private sector. It is estimated that the public sector covers about 83% of the population. Low-income individuals (≤€15,400/year), chronically-ill patients, and civil servants are eligible for public-sector coverage. In the private sector, almost all costs paid out-of-pocket, with a small part reimbursed by voluntary health insurance. In 2010, 41.5% and 58.5% of health expenditure was publicly and privately funded, respectively (Theodorou *et al* 2012). The country expects to introduce a universal health insurance coverage in 2016 (Antoniadou 2005; Cylus *et al* 2013). The speed of implementation will in part depend on the time needed to adapt the relevant pharmaceutical policies, as outlined in this report.

At the request of the Cyprus Ministry of Health (MoH), the World Health Organization (WHO) Regional Office for Europe will support the MoH with enhancing the pricing and reimbursement systems. In the public sector, a tendering system is in place that achieves relatively low drug prices. In the private sector, however, there are considerable challenges with the pricing of pharmaceutical products; there are also potential access issues for imported pharmaceutical products, as well as pricing issues for locally manufactured or packaged products, particularly as a significant proportion of the latter is being exported.

A WHO mission took place on April 1-4, 2014 where the authors of this report met with key stakeholders. All meetings were held at the Headquarters of the Pharmaceutical Services of the Ministry of Health in Nicosia, Cyprus, with the following groups: Health Insurance Organisation, Cyprus Pharmaceutical Association, Cyprus Association of Research and Development Pharmaceutical Companies, Cyprus Pharmaceutical Companies Association, Cyprus Pharmaceutical Manufacturers Association, Pharmaceutical and Chemical Manufacturing Company, and Cyprus Federation of the Patients Associations. Meetings were also arranged with the Minister of Health, Dr Philippos Patsalis, and the Acting Director General of the Ministry of Health, Dr Christos Kaisis.

Overall, the objectives of this mission were to (a) determine whether prices for prescription pharmaceuticals in the public sector (tender system and negotiations) are optimal and in the public interest for the Cypriot government; (b) determine whether prices for prescription pharmaceuticals in the private sector (determined through

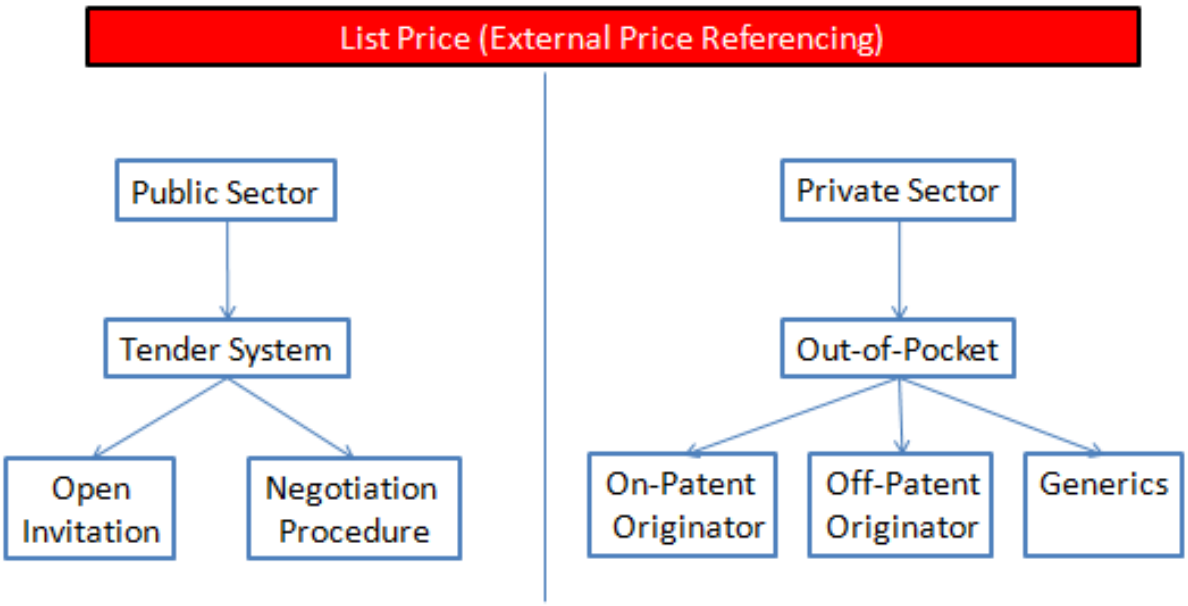
external price referencing) are affordable for consumers/patients; (c) comment on how the public and private systems can be fused into one when health insurance will be implemented; and (d) provide a roadmap for health insurance implementation including an outline of the preparatory steps that need to be undertaken prior to full implementation of health insurance.

Towards these aims, the report first reviews the current system for pharmaceutical care, reflects on the stakeholder views, and summarises the challenges. Next, it proposes short-term policy options to improve the regulatory framework from an access to medicines perspective (i.e. availability and affordability), focusing mainly on the supply-side (pricing and reimbursement) but also making proposals for the demand-side that the competent authorities can implement before health insurance takes effect. Then, the report provides a roadmap of actions that need to be fulfilled prior to health insurance implementation, as well as a number of challenges that need to be addressed following the introduction of the new insurance scheme.

2. Current pharmaceutical policies and expenditure in Cyprus

In 2011, pharmaceutical expenditure accounted for 19.8% of total health expenditure (Mercer 2013), including private and public sector spending on prescription (inpatient and outpatient) and over-the-counter drugs. Based on 2011 figures, total pharmaceutical spending per capita (€322) is below the EU average (€349), although it differs markedly between the public and private sectors. In 2011, €106.8 million (50.5%) and €104.5 million (49.5%) were spent in the private sector and public sector, respectively, despite the private sector serving less than 20% of the population. Per capita spending on drugs in the private sector is among the highest in the world. The pricing policies in Cyprus are reviewed every four years by the Medicinal Products Price Control Committee and, if needed, amended by the Minister of Health based on this review. The following sections present the current policies used to control prices in the public and private sector (*Figure 1* presents a general schematic).

Figure 1. Cyprus pharmaceutical market: public and private sectors



Source: The authors.

2.1. The public sector

All drugs sold in the public sector are listed on a positive formulary, which currently includes 1,767 products. Notably, nearly all cancer, haemophilia, hepatitis B and C, immunosuppressive, anti-TNF, and HIV drugs are sold exclusively in public pharmacies, as these patients are eligible for public coverage. An initial list price is calculated

through external price referencing (EPR). The features of the EPR system are described in greater detail in the next section on the private sector.

Public sector drugs are procured centrally by the Department of Pharmaceutical Services of the MoH through international tenders to try to achieve additional discounts to this EPR list price. The international tenders award the right to a single firm to supply the whole market for the particular category that is being tendered. The government procures the entire quantity of drugs in three or four instalments, and the firm is reimbursed upon delivery of the drugs. The procured drugs are distributed to public pharmacies, which include 11 hospital pharmacies and 34 outpatient pharmacies. The annual storage, distribution, and dispensing cost for outpatient drugs are about €6.3 million. *Table 1* summarises the 2013 drug expenditure in the public sector. In the public sector, the ten best-selling product (*Table 2 - Appendix*) account for 17.6% of total drug spending, while the top 50 products account for 44.0%.

Table 1. Drug expenditure in the public sector (2013)

Category	€, millions*
Total drug expenditure	103.5
Prescription drugs	98.5
Inpatient	59.5
Outpatient	39.0
Over-the-counter drugs	5.0
Outpatient drugs	
On-patent originator	7.7 (19.7%)
Off-patent originator	10.8 (27.6%)
Generics	19.3 (49.5%)
Vaccines and others	1.2 (3.2%)

* These sales figures do not include value-added taxes.

Source: Data obtained from the Pharmaceutical Services, MoH, Cyprus**.**

About 75% of public sector drugs are tendered through an open invitation that applies at the molecule level, although in some cases tenders are at the therapeutic level; the entire procedure lasts approximately eight months, excluding delivery time, and accounts for about €54.5 million in public-sector sales. The remaining 25% of public tenders consist of negotiations or other processes (e.g. accelerated procedures), which last about one month; this channel is mostly reserved for specialised products, such as oncology drugs, and accounts for about €50 million in sales.

The public sector tendering system achieves substantial price reductions for multi-source drugs, or drugs that are manufactured by multiple firms (e.g. originator and generic drugs, or other therapeutically-equivalent drugs). Usually, the tender prices are 60-80% lower than those found in the private sector; for generics with small market size the difference is usually ~20%. In extreme cases, public tenders result in prices that

are over 3,000% lower than the private sector EPR prices. For single-source drugs, such as on-patent drugs with no therapeutic substitutes, the public sector prices are usually marginally lower (~5-10%) than those in the private sector. This result is logical in the absence of competition from other manufacturers for these products (*Table 3 - Appendix*). The Ministry of Health currently does not negotiate further price discounts on the basis of willingness-to-pay or other pharmacoeconomic criteria.

Table 2. Top 10 products in the public sector by sales value (2013)

(Appendix)

The legislative framework underpinning tendering is transparent and has remained stable for about 30 years. All tender outcomes are made publicly available, including the tender price and the total contract value. Once a tender price has been accepted by both the MoH and the manufacturer, the price cannot be adjusted as these agreements are legally binding.

Table 3. Tender and list prices (EPR) of four medicinal products, 2013

(Appendix)

2.2 The private sector

Although about 5,241 products are registered for sale in the private market, only 2,054 are currently available, mostly due to insufficient demand for the other products. There are 481 private pharmacies in Cyprus (~1 per 500 persons). Prices in the private sector are set by the MoH, based on the recommendations of a Pricing Committee. The Committee relies on EPR to suggest a domestic price. The prices are based on the average wholesale prices in a basket of four countries consisting of one high-price country, two medium-price countries, and one low-price country. The reference countries are presented in *Table 4* and are selected in the order they are listed; if a drug is not available in a country, the next country in the list is chosen. The wholesale prices in reference countries include the wholesaler margins and distribution costs. If only the retail or ex-manufacturer price of a drug is available in a reference country, formulas are used to convert it to the wholesale price. For non-euro prices, the annual average exchange rate from the previous year is used to convert the prices to euros. A 3% mark-up is added to the EPR price to cover the cost of importing drugs to Cyprus.

Table 4. Reference countries for external price referencing (2012)

Category	Reference countries	Alternates
High-price	Sweden	1. Denmark 2. Germany
Medium-price	Austria and France	1. Italy 2. Belgium
Low-price	Greece	1. Spain 2. Portugal

EPR prices are updated every two years with the price changes coming into effect on January 1st of the relevant year. The prices are calculated six months in advance and announced three months before the price is changed. The price revisions only apply to drugs with wholesale prices greater than €10, while the prices of all other drugs remain unchanged. National legislation also outlines contingency plans if prices are not available in all reference countries. Alternative pricing calculations are also used for products with a maximum wholesale price equal to or less than €6 or an annual volume of sales less than €25,000, with the aim to balance the need for both low prices and drug availability.

Table 5. Pharmacy margins in the private sector (as of February 2013)

EPR list price (X)	Margin
X ≤ €50	37%
€50 < X ≤ €250	33%
€250 < X	25%

The retail prices charged by pharmacies include pharmacist mark-ups and value-added taxes (5%). The pharmacist margins in the private sector are summarised in *Table 5*. Although these markups are regressive, they usually encourage the dispensing of more expensive products. Pharmacists also receive a flat fee of €1.00 per prescription (dispensing fee). *Table 6* summarises the drug expenditure in the private sector (2013). The annual distribution and dispensing cost for outpatient drugs is about €28.9 million. In the private sector, the ten best-selling product (*Table 7 – Appendix*) account for about 11.5% of total drug spending, while the top 50 products account for 34.5%.

Table 6.Drug expenditure in the private sector (2013)

Category	€, million*
Total drug expenditure	94.9
Prescription drugs	80.6
Inpatient	6.9

Outpatient	78.0
Over-the-counter drugs	14.3

Outpatient drugs	
On-patent originator	8.4 (11.8%)
Off-patent originator	46.6 (65.7%)
Generics	11.4 (16.1%)
Vaccines and others	4.5 (6.4%)

- These sales figures do not include value-added taxes.

Source: Data obtained from the Pharmaceutical Services, MoH, Cyprus**.**

Compared to the public sector, generic drug consumption remains low in the private sector, largely because pharmacists are not allowed by law to substitute generics for originator drugs prescribed by physicians. In addition, generic prescribing by international non-propriety name (INN) is not explicitly required or encouraged. In the private sector, physicians are independent and prescribe autonomously without being monitored by any governmental body. The government does not intervene with binding protocols or targeted prescribing guidance, which is also uncommon in the public sector. There are few limits on the physician detailing and advertising activities of pharmaceutical firms.

For generic drugs, Cyprus applies a price cap of 80% of the wholesale EPR price. In cases where a generic drug is available without the originator drug having been marketed in Cyprus, the Pricing Committee relies on EPR to set the generic drug price. Cyprus and the Czech Republic are the only EU member states that rely on foreign list prices to set domestic generic drug prices. As a result, the Cypriot generic drug prices are among the highest in Europe, as the EPR system is not able to capture any confidential discounts on generics in other countries. In other words, by relying on the list prices instead of transaction prices in other countries, the Cypriot consumer is vastly overpaying for generic drugs.

Table 7. Top 10 products in the private sector by sales value (2013)

(Appendix)

3. Stakeholder views on current pharmaceutical policies

In the context of the WHO mission, a number of stakeholders were invited to attend meetings with the authors at the headquarters of the Pharmaceutical Services. The authors met with the following stakeholders: (a) Health Insurance Organisation, (b) Cyprus Pharmaceutical Association (representing pharmacists), (c) Cyprus Association of Research and Development Pharmaceutical Companies (KEFEA) (the research-based manufacturers), (d) Cyprus Pharmaceutical Companies Association (representing importers and distributors), (e) Cyprus Pharmaceutical and Chemical Manufacturing Company (representing local manufacturers), and (f) Cyprus Federation of the Patients Associations. The key takeaways from these meetings, as well as the stakeholder positions, are briefly outlined in the following sections.

3.1. Health Insurance Organisation

Under the new national health insurance scheme, there will be a common source of funding and budgetary constraints. Global budgets will be introduced, which will represent absolute ceilings, and the organisation will have no borrowing capacity. The budget will be divided between the different elements of health spending, including inpatient (hospital) care and pharmacologic treatment. The Health Insurance Organisation (HIO) has been working closely with consultants to design the new system and outline the preparatory steps that will need to be introduced prior to 2016. They have prepared a draft document with policies regarding drug reimbursement and pricing, formulary management, etc. The aim of HIO will be to decrease prices and stay within the budget, while also ensuring market access to new, innovative drugs. In the new system, there will be a separation of outpatient and inpatient care, with the latter internalised in the system of diagnostic-related groups (DRG).

The HIO representatives stressed the need to lower drug prices in the short-term, before the new system is introduced, and to also consider long-term options, such as risk-sharing (e.g. price-volume agreements) and other reimbursement strategies. A regressive mark-up or flat fee for pharmacists should also be introduced to disassociate the income of pharmacists from the drug price and to increase generic drug consumption In addition, mandatory INN prescribing and generic substitution will be introduced. As the consumption of out-patient medicines is likely to increase, it is important to increase generic drug use. However, as previously mentioned, pharmacist margins cannot be adversely affected by lower prices.

The 80% rule for generics is inefficient and substantially lower prices can be achieved through reimbursement strategies, such as internal reference pricing. Therapeutic internal reference pricing is the preferred option, although exceptions will be needed in some classes where it cannot be easily implemented. Generic drug use is high in the

public sector and it will be important to cultivate a similar culture of high public awareness of generics (e.g. about bioequivalence) in the unified system.

For on-patent products, negotiations should predominate and tendering should be limited to generic drugs. However, tendering should be used to establish a price, not purchase drug stocks, as is done in Sweden and Denmark. An e-prescribing system is needed to monitor and enforce prescribing behaviour. In addition, the remuneration of physicians will be changed to prevent frivolous care and prescribing habits (e.g. capitation system and pay-for-performance). Co-payments for drugs are needed, with exemptions for vulnerable patients groups (e.g. elderly, chronically ill, etc.). The HIO would like to introduce a flat fee for drug dispensing and also make patients pay for the difference between the internal reference price and higher drug prices. The idea was based on studies of other small European systems (e.g. Austria, Czech Republic, etc.). The HIO is also considering a 0% co-payment for diseases where compliance is an issue, such as psychiatric disorders. Also, there will be a maximum annual co-payment that patients can contribute; this ceiling will include out-of-pocket spending on all health care, not just drugs.

Importantly, more studies are needed to understand how demand of health care and drugs will change under the new system. However, HIO believes that even if demand for health services increase, the average cost per service should decrease. General practitioners will also serve an important role as gatekeepers to limit unnecessary visits to specialists.

Overall, under the unified system, the HIO acknowledged that the current private prices are unaffordable. To maintain current expenditure levels the prices will need to decrease and the current spending amount should serve as a benchmark. However, it is important to recognise that manufacturers will not have access to parallel markets in the new system to cross-subsidise profits. Therefore, policy changes will need to be carefully considered to guarantee availability for patients. The HIO is currently in the process of updating and adjusting its road map to submit to parliament within 2014 for the implementation of the national health system.

3.2. Cyprus Pharmaceutical Association

The Cyprus Pharmaceutical Association, which represents pharmacists, is hopeful that a national health system will be implemented. This would increase the number of patients that private pharmacies serve and, therefore, alleviate some of the financial strain on pharmacists and ensure the continued availability of drugs. The association would also like to increase the number of pharmacies given the increased demand they would face under a unified system. There are currently 481 private pharmacies that cover all geographic areas, corresponding to about one pharmacy per 500 private sector patients. The organisation also endorsed the implementation of reimbursement strategies to

control drug expenditure, which would introduce added flexibility, and also supported mandatory INN prescribing.

There are currently insufficient profits in the public sector and pharmacists focus on sales to the private sector. According to the association, the pharmacy business is under severe strain and some pharmacies are closing due the lack of profits; still, there is a net increase in the number of new pharmacies [*Authors' note*: this implies that the outlook for the profession is positive, especially considering the prospect of universal health insurance implementation]. To compensate for lost profits, some pharmacists have expanded their roles to provide medical advice, conduct blood tests (e.g. glucose readings), and sell cosmetic and baby products. However, the association stressed that the primary role of pharmacies should remain the dispensing of prescription drugs. By diversifying their services, they are getting farther removed from their intended and most important task.

The association's view on prices was that it would be important to ensure that private sector prices do not decrease sharply, which could harm profitability and could lead to product shortages. The association highlighted recent experiences in Bulgaria, where sharp price declines threatened the availability of medicines, especially for innovative products.

3.3. Cyprus Association of Research and Development Pharmaceutical Companies (KEFEA)

The organisation, which represents research-based manufacturers, expressed a desire to continue being a valuable partner to the Cypriot authorities. KEFEA would like to contribute through policy suggestions to build an efficient and sustainable system that will ensure equitable access to innovation for all Cypriot patients. The organisation would like to explore, with the support of the European Federation of Pharmaceutical Industries and Associations (EFPIA), the implementation of risk-sharing agreements to mitigate budget pressures. Importantly, KEFEA stressed the need for confidential prices to offer price discounts. When prices are transparent, it is more difficult to reduce the spill-over effects of low prices. Therefore, KEFEA advised Cyprus to separate the pricing and reimbursement functions of the MoH. This will allow manufacturers to lower the real prices but maintaining high list prices, which maximises coverage while protecting manufacturers' interests in other markets.

Although the overall pharmaceutical expenditure in Cyprus is comparable to other OECD countries, the private sector per capita spending is one of the highest in the world; this most reflects a price effect, rather than a volume effect. As a result, some vulnerable patients are hurt, and KEFEA agrees that steps should be taken prior to the implementation of the national health system to alleviate the out-of-pocket burden on

patients. However, it is important to consider the health system (macro) perspective when changing the pricing system.

In the interim, the organisation suggested that Cyprus re-evaluate drug prices through the EPR system annually, instead of every two years. KEFEA conducted preliminary analyses and estimated that if the country re-calculated prices with the same basket of countries, the private-sector prices would decrease by 5%. To arrive at this estimate, five research-based manufacturers (Merck Sharp & Dohme, Novartis, Pfizer, Sanofi, GlaxoSmithKline) selected five anonymised products (one pack size per product), collected the current list wholesale prices (as of 25 Feb 2014), estimated revised wholesale prices if EPR were applied today (Mar 2014 prices), and calculated the price differences for each product. The estimated price changes ranged from -52% (Novartis product A) to +5% (GlaxoSmithKline product C). This corresponded to an overall net decrease of 5% when averaged across all products. [*Authors' note*: Based on our review of the calculations, it is not clear how the products were selected and whether these findings are generalisable across all drugs and pack sizes sold in the country].

KEFEA also acknowledged that EPR only captures list prices in other jurisdictions, not the actual transaction prices. Cyprus is therefore not obtaining the discounts other countries are achieving. KEFEA suggested that additional savings can be generated through lower generic drug prices. These savings could be used to re-invest in originator products to stimulate innovation. To achieve savings, it is necessary to implement reimbursement policies, which are currently not available.

3.4. Cyprus Pharmaceutical Companies Association

This organisation, which represents Cypriot importers, is in charge of the distribution or wholesaling of drugs in Cyprus. It is also responsible for some pharmacovigilance activities, but not marketing or retailing. The organisation represents a variety of originator and generic manufacturers and is in essence a logistics provider. In most cases, there is one distributor per manufacturer through exclusivity deals; most generic products are imported from various EU countries.

Given the small market size, the Cypriot importers stressed the need to balance aggressive pricing policies with availability concerns. In particular, the private sector represents a very small proportion of the country. Therefore, a sharp price decline in the private system could jeopardise the profitability of drug importation and lead to drug shortages if products are priced below €20-30 according to the association.

The organisation welcomes the transition to a national health insurance system which will expand the patient base, but would like to continue to apply the current private-sector pricing system. Still, the association believed that they could obtain better prices from manufacturers in response to a larger patient population under the new system

(i.e. if manufacturers would like to be included in HIO formulary). For example, bilateral negotiations between payer and firms could be mediated through the Cyprus Pharmaceutical Companies Association. This will be necessary to compensate for the extremely high expenditure per capita in the private sector and for Cyprus to maintain spending levels that are comparable to other OECD countries.

3.5. Cyprus Pharmaceutical and Chemical Manufacturing Company & Cyprus Pharmaceutical Manufacturers Association

The Cyprus Pharmaceutical and Chemical Manufacturing Company represent local manufacturers of generic products. The active ingredients are often imported from India, China, and other European countries. A large percentage (90-93%) of the products produced by Remedica and Medochemie (two of the main local manufacturers) are destined for exports. The quantity of exports is increasing and the domestic list price in Cyprus is therefore an important determinant of success in export destinations. According to the organisation, the importing countries (e.g. Egypt, Jordan, Lebanon, and Saudi Arabia) often request data on the Cypriot prices to compare the price at which they are importing the products.

Of the 7-10% of products sold in Cyprus, about 50% are sold in the private sector and 50% in the public. In the public sector, the prices achieved for generic drugs are very low. In the private sector, prices are substantially higher, which is necessary to sustain the exporting business. The organisation stressed the need for the Cypriot authorities to support their exporting business and to mitigate the spill-over effects of domestic policies on drug sales abroad. Also, the government should speed up the registration of new products and the approval of prices to minimise the delay in time to entry.

3.6. Cyprus Federation of the Patients Associations

The organisation stressed the importance of comprehensive coverage and choice of medicines for all patients, especially orphan drugs. The equitable access to medicines is of paramount importance to the organisation. In this context, it argued that the choice of medical treatment must remain with the prescriber, not the pharmacists. There are also psychological barriers to generic drug use that should be considered, especially if drug features, such as the shape, colour, and size, changes every two years following a tender. The physical characteristics of the medicines may adversely influence adherence rates. More generally, communication and involvement is vital to ensure that patients feel included in the reform process. A transparent process is necessary to obtain the acquiescence of patients.

Due to the perceived inferior quality of generic medicines, patients are willing to pay considerably higher prices for originator ("brand") products. The association agreed

that it is important to educate patients about the bioequivalence of generic and originator products. In addition, it would be advisable to continue to offer the originator after patent expiry, but force the patient pay the difference between generic and originator price to promote generic use. More generally, a greater emphasis on prevention and prophylactic interventions should be given to minimise the need to take medicines. A proactive approach to healthcare with an emphasis on preventive care, rather the current reactive paradigm, is more sustainable for the Cypriot health system in the long-run. In the meantime, however, it is necessary to meet the needs of all patients, especially chronically-ill ones. For patients, the access to medicines perspective (affordability/availability) is the most appropriate when assessing the performance of the regulatory policies for medicines.

4. Summary of key issues in the Cypriot pharmaceutical market

The pharmaceutical market in Cyprus is characterised by a number of peculiarities and challenges. These country- and system-specific issues are outlined below.

4.1. Market size

Cyprus suffers from what is known as the 'small market' problem. As generics are an effective way to encourage more rational use of medicines and contain pharmaceutical expenditure, the lack of marketing in individual countries with small markets is an issue that should be addressed by national authorities. A small market like Cyprus ought to provide incentives to generic development and marketing, such as:

- Promotion of generic prescribing linked with financial incentives;
- Tender contracts should not be awarded for an excessive period of time; and
- Mandatory generic substitution for pharmacists linked with possible financial benefits for pharmacists to dispense generics

However, these measures could have substantial implementation costs, which should be carefully evaluated prior to any reform by reviewing previous experiences – when available – and by carrying out prospective impact analyses. If the policies are implemented, the competent authorities should continue to monitor the results.

It could be the case that registration requirements could be optimised, e.g. adjust language of the labelling and the leaflets to those of larger neighbouring countries, as this might reduce investment costs for generic manufacturers and encourage product launch. Examples of countries that have done so are Malta (to UK) and Luxembourg (to Belgium). Additionally, if the cost of marketing a medicine in a small country is higher than in a larger market because of the production of small batches or delivering small orders, it might not be feasible to impose local prices at the same or at a lower level than those of larger markets. This is also a frequent criterion in the context of price regulation based on external price referencing, unless the small country's cost differential is subsidised or compensated.

4.2. Pricing

A number of items have emerged with regards to the pricing system in Cyprus. External price referencing, which has been applied in Cyprus since 2005, is associated with numerous short- and long-term shortcomings. Notably, EPR schemes are unable to capture negotiated discounts in other countries, and may therefore lead to inefficient and inequitable pricing outcomes. Specifically, EPR may represent a regressive pricing scheme, whereby lower-income, smaller countries with limited negotiating power pay higher prices than higher-income, larger countries. In schemes where multiple

currencies are referenced, exchange rate volatilities can have a greater effect on prices denominated in local currencies than what is attributable to actual price movements.

In addition, the Cypriot EPR system has two specific issues. The first is the inability to capitalise on (confidential) discount arrangements with manufacturers on the prices of expensive niche products, which account for a substantial proportion nearly 50% of total public spending on pharmaceuticals. As all prices in the public sector are (potentially) publicly available, manufacturers are not willing to provide substantial price reductions as these might influence their profits in foreign jurisdictions. A more opaque negotiation process is needed for the MoH to realise greater savings, particularly for on-patent products in the public sector. The second shortcoming is the length of time between price revisions, which is currently two years. This does not enable the Cypriot authorities to take advantage of price revisions in the basket countries, which would result in lower (list) prices for the private sector.

The private sector prices are high and the burden is borne by patients. This can lead to salient affordability issues and may even deter some patients from seeking pharmacologic treatment. Given the current economic climate the decreased purchasing power of the average Cypriot patient, downward pricing changes would ensure more affordable prices for the private sector.

4.3. Reimbursement

Perhaps the single most important challenge of the pharmaceutical sector in Cyprus is the absence of a health insurance scheme and the resulting lack of a reimbursement system that accounts for the peculiarities of the local market. Without a reimbursement system, the country is unable to exercise any form of market power by implementing tools that are used in most other EU member states (e.g. an integrated generics policy linking pricing with prescribing, dispensing, and cost-sharing). The absence of reimbursement for the entire population may also create access problems (in terms of both affordability and availability of certain drugs) to those who are not eligible for publicly funded pharmaceutical care. While the level of coverage for expensive therapies, catastrophic care, and in-patient care is considered to be adequate, the lack of reimbursement in the outpatient segment exposes citizens to undue financial and health risks.

The lack of a reimbursement system results in a further shortcoming, as it does not allow decision-makers to establish preferential rules for the reimbursement of specific products (e.g. expensive niche therapies). This could be achieved through arrangements that maintain list prices fixed, but negotiating on reimbursed prices on a confidential basis. A further challenge arising from the lack of a reimbursement policy is the inability to implement rational prescribing, which may also relate to the positioning of individual therapies in the context of a disease pathway (i.e. first or second line treatment, etc). It

may therefore be the case that treatments that are meant to be second line therapies are offered as first line therapies, with obvious implications for out-of-pocket expenses.

Also, given the current economic climate the decreased purchasing power of the average Cypriot patient, pricing changes are needed to ensure that the private sector prices decrease. In addition, greater use of low-priced generic drugs is needed in the private sector.

4.4. Prescribing

Currently, there are no mechanisms in place to monitor and control the prescribing behaviour of physicians. Coupled with brand awareness, this has led physicians to potentially over-prescribe on-patent, expensive products with no fear of financial or non-financial penalties. Clinical protocols, if they exist, are in the majority of cases too general to steer prescribing clinicians in a particular direction. Issuing prescribing guidance would only make sense if there was a reimbursement agency to enforce it, which is currently not the case in Cyprus. In the presence of universal health insurance, a key task would be to ensure that electronic prescribing is linked to prescribing guidance to ensure rational and cost-effective use of medicines. The medical profession should participate in this process and consult the international published evidence in the field. There is pressing need to introduce an electronic prescribing system to curb and eventually reverse these trends. Improved IT infrastructure is a prerequisite to achieving appropriate and rational prescribing.

4.5. Provision of information and advertising

It is essential to break any financial relationships between physicians and pharmaceutical manufacturers or the pharmaceutical supply chain. The detailing activities of manufacturers should be controlled. Both manufacturers and the medical profession can self-regulate by adhering to a widely publicised code of practice. The government should also regulate the number and types of samples or other benefits received (e.g. the number of sponsorships to conferences overseas, etc.), among other factors. Most other EU countries have introduced strict limits on the gifts and contributions that physicians can receive from private entities. Having a tight reimbursement system with prescribing and dispensing checks will also gradually remove conflicts of interest, or outright corruption. Consequently, the government and health insurance should provide the necessary information that clinicians need in their daily practice and information.

4.6. Dispensing

Despite the recent introduction of a – broadly speaking – regressive remuneration structure, the current payment scheme for pharmacists in the private sector still favours the dispensing of expensive, on-patent products. Pharmacists have the incentive to dispense more expensive products given they are paid on a flat percentage within a broadly defined price band. At the same time, there is no legislation about generic substitution. It is usually the combination of financial incentives (e.g. regressive mark-ups or flat dispensing fees) and enforcement (e.g. mandatory generic substitution) that increase generic consumption. Ideally, Cyprus should transition to a reimbursement system where the income of pharmacists is disconnected from the prices of drugs. This is particularly important if the prices of generic products are further decreased and higher generic consumption is promoted. To compensate for this decrease in drug expenditure, pharmacists' incomes should be safeguarded from these pressures. This can be achieved through a series of pilot schemes with the backing of the pharmacists' association.

4.7. Cost-sharing

There is currently little cost-sharing in place in the public sector, whereas private sector patients pay for their drug costs out-of-pocket. There is a small-scale co-payment plan that has an annual budget of €600,000 and applies to a limited number of products in specific therapeutic groups. The plan is available to public beneficiaries to access medicines that are only available in the private sector. The government pays the difference of the corresponding treatment by an average (grouped) percentage (or, in one case, a flat fee).

When introducing universal health insurance coverage that also includes a prescription drug benefit, there will be a need to address he system of cost-sharing in a holistic way in order to ensure that the burden on patients is reduced by the simultaneous introduction of co-payments. Proposals to that end could include, for example, a flat fee with exemption clauses for vulnerable patient groups.

4.8. Perceptions of different pharmaceutical products

Currently, brand awareness in the private sector is high and patients raise doubts about the value and benefits of generic drugs. As a result, generic penetration in the private sector is very low. Beyond raising awareness about the benefits of generic medicines, integrated generic policies (e.g. internal reference pricing and policies aiming at prescribers and pharmacists) are needed to ensure that patients are price sensitive. Education campaigns are needed to show patients and physicians the value of generic drugs.

4.9. Overall

The current system incentivises the use of branded drugs in the private sector. Prices are high in the private sector and low in the public sector (the component of me-too drugs and generics). Prices for on-patent drugs in the public sector are also high as the level of discount given to the state is small. The Cypriot authorities need to consider whether price reductions can be achieved in the short-term without upsetting a delicate balance that enables the market to function properly without supply issues.

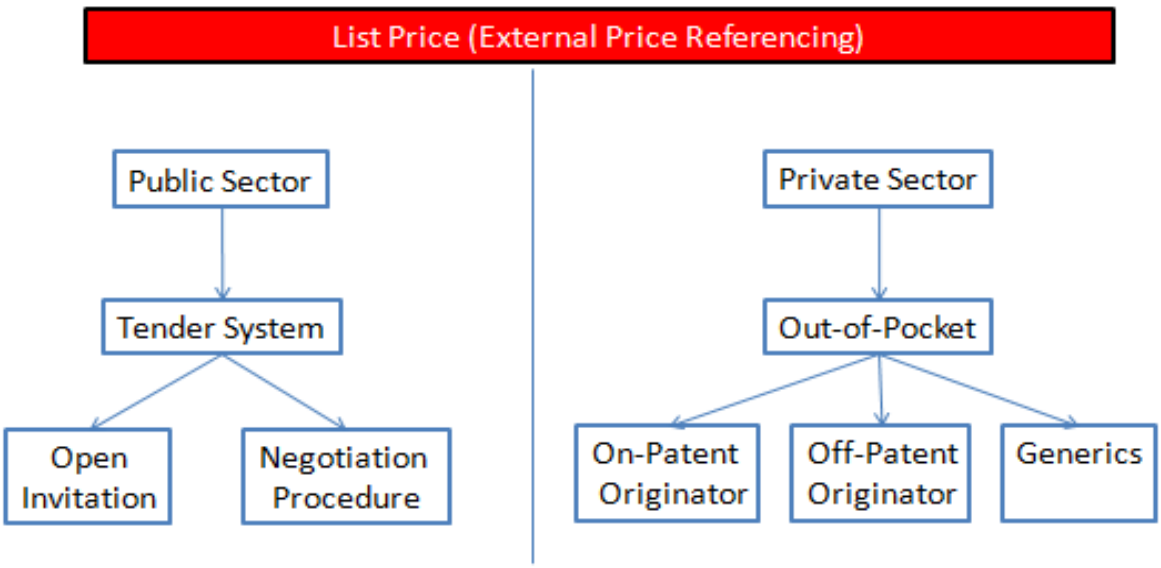
5. Pharmaceutical policy in the short-term: Policy options

5.1. The rationale for the options outlined and assumptions behind them

The analysis in the previous sections suggests that it is possible to realise sizable efficiency gains in the Cypriot regulatory system for pharmaceuticals in both the public and private sectors. For products that are available in both sectors, the current system enables manufacturers to price discriminate based on whether a product is intended for sale on the public or private market. In effect, the fragmented system allows firms to cross-subsidise low profits in the public sector with high prices in the private sector, where patients pay for drugs out-of-pocket.

The short-term recommendations proposed in this section are structured to address supply-side challenges in each of the five distinct market segments: the (1) open invitation and (2) negotiation procedure in the public sector, as well as the (3) on-patent originators, (4) off-patent originators, and (5) generics in the private sector. These recommendations constitute temporary solutions that will be reviewed once the country's economic situation improves. The recommendations should also serve a transitory role in preparation for the switch to a unified national health insurance system.

Figure 2. Market segments in the Cypriot pharmaceutical market



In making the recommendations in the sections that follow, we have taken into account: (i) the insights obtained in meetings with the competent authorities (Ministry of Health, Pharmaceutical Services, Health Insurance Organisation) and the range of stakeholders; (ii) the peculiarities of the Cyprus pharmaceutical market in terms of its small size and its division into the public (tender) and private (out-of-pocket) markets; (iii) the fact that although the Cypriot market is divided between the public and the private sector markets, the two are inter-connected and interventions on one part of the market may

have significant impact on the other part; (iv) the need to maintain a balance so that the market continues to be supplied and no shortages occur; (v) the fact that the available budget for pharmaceuticals by the public sector has been reduced in 2014-15 by 15%; (vi) the increasing cost of niche therapies and their contribution to the total cost of pharmaceuticals; (vii) the lack of a distinct reimbursement policy for the private sector, whether on the supply- or on the demand-side, and the fact that the public sector covers the needs of eligible patients with a single tool/process (tenders through open invitation or negotiation); and (viii) the introduction of generalised health insurance in the foreseeable future.

Box 1. Summary of pharmaceutical policy options for the short-term

A. Supply-side

1. Pricing system options
   - External price referencing system: modest wealth adjustment to current price levels
   - Public sector open invitation procedure: watchful waiting
   - Public sector negotiation procedure: negotiations with manufacturers the outcome of which will remain confidential
   - One of the following price adjustments: (a) across-the-board price cut of up to 8.5%; (b) Off-patent originator medicines: across-the-board price cut by 20-30% and continue linkage of generic prices to originator brands at 80%; and (c) re-calibrate the way prices are calculated, either based on the lowest price in the current basket, or by changing the reference countries in the basket to countries with lower prices

2. Other interventions related to the pricing system
   - Introduce annual price revisions (instead of every two years)
   - Introduce a one-off rebate in 2014 based on 2013 sales to the public sector; the calculations should be based on the market shares of individual manufacturers (i.e. average of 4-5%)

3. Other supply-side interventions not related to the pricing system
   - Implement a regulatory framework for advertising activities for pharmaceutical manufacturers and distributors and initiate self-regulation by relevant stakeholders
   - Re-define the role and the makeup of the pricing committee to include institutional stakeholders and technical experts

B**. Demand-side**

4. Introduce prescribing guidance in the public sector

5. Consider tendering at therapeutic class level

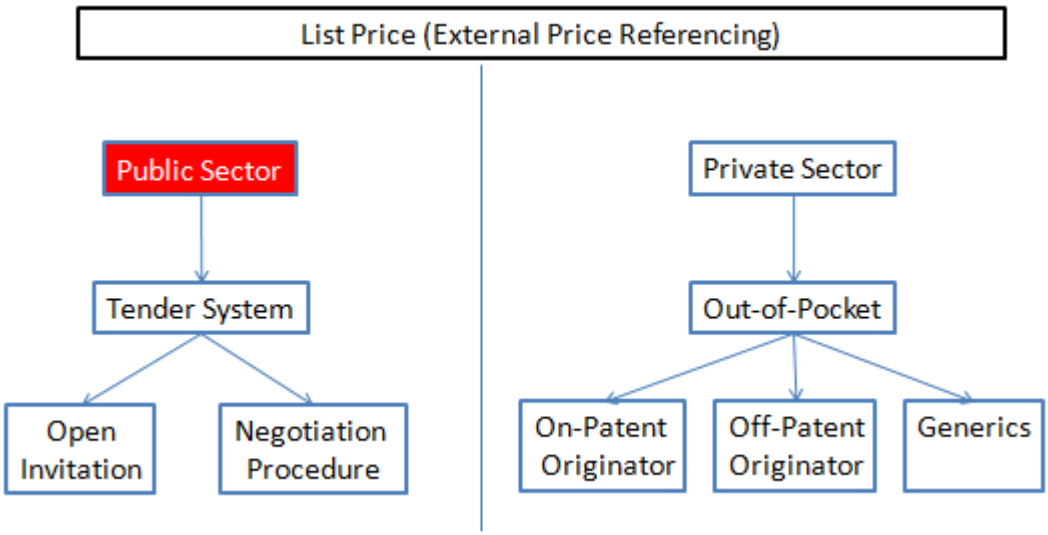
6. Undertake a campaign to improve the perception of generic medicines among prescribers and the general public

7. Re-visit the upper ceiling of pharmacy remuneration with a view to rationalising it downwards and ultimately disconnect pharmacy income from medicines' pricing

5.2. The supply-side: The public sector

The public sector tender system is divided into (a) the open invitation procedure, whereby suppliers are invited to submit bids which are subsequently evaluated and awards are made for the totality of the market based on the lowest price submitted, and (b) the negotiation procedure, whereby manufacturers are invited to a process of negotiation based on an ex-ante fixed volume. The open invitation procedure is predominantly meant for drugs whose patents have expired, and therefore there is a potential for competition from generic manufacturers. For new drugs that are patent protected, the negotiation procedure is applied. A schematic presentation of the public sector sub-segments is shown in Figure 3. As the two segments within the public sector system address two different types of medicines (off-patent and generics in the open invitation system and on-patent niche drugs in the negotiation procedure), interventions in each segment may vary.

Figure 3. Public sector pharmaceutical market segment and its components

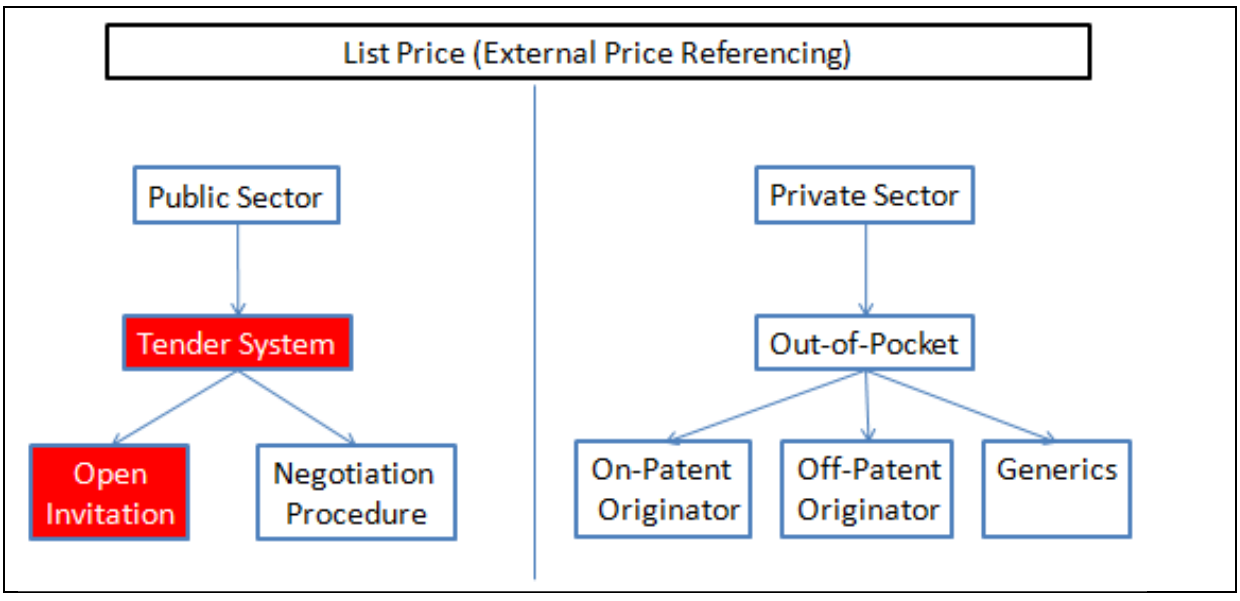


5.2.1. Open invitation procedure

Assuming that the list prices determined through EPR remain unaffected, it is unrealistic to expect that further savings can be achieved through the open invitation procedure alone. This conclusion is based on a review of tender prices across a range of 42 molecules, which were included in several tender documents and three key facts: first, our review of available tender data suggests that for molecules with large market size, competition is significant with several competitors participating and submitting bids; competition is, however, less prominent in molecules with small market sizes (see Table 3). This is consistent with the evidence from other EU countries (e.g. Netherlands and Germany). Second, the price range between highest and lowest bids, particularly for molecules with large market size, is also significant (8- to 11-fold depending on the case), showcasing the difference between (originator) brands and generics. And, third, the price difference between the list price and the tender/bid price is also significant, highlighting the fact that the tender price brings the winning bid closer to the reservation price or marginal cost of production. Unit prices achieved through the tender system and for the molecules reviewed are comparable to those achieved in other European settings based on the available literature (Kanavos et al, 2009, 2012).

The system currently operates within the context of a clear legal framework with precise provisions about process, timelines, and the subject of the negotiation. Currently, quantities tendered are estimated for two-year tender cycles based on consumption levels in the previous year(s). To ensure transparency and equity, the legal framework is very explicit on the timing to be followed in each case and gives one calendar month to both parties to conclude a negotiation (described in the next section). The outcome of this process is made publicly available in the official gazette.

Box 2. The open invitation segment in the public pharmaceutical market segment



Recommendation 1

We recommend "watchful waiting" and that the MoH continue to implement the current tender system, which is state of the art and has delivered significant benefits over time. It is unlikely that the tender system (open invitation) will deliver better prices or lower total cost to the public sector over the short-term. Further rationing of expenditure in the public system under current conditions could only be achieved by studying how volume is determined, or by altering prescribing habits through demand-side interventions; demand-side measures, however, would be difficult to implement in the short-term in the current system.

5.2.2. Negotiation procedure

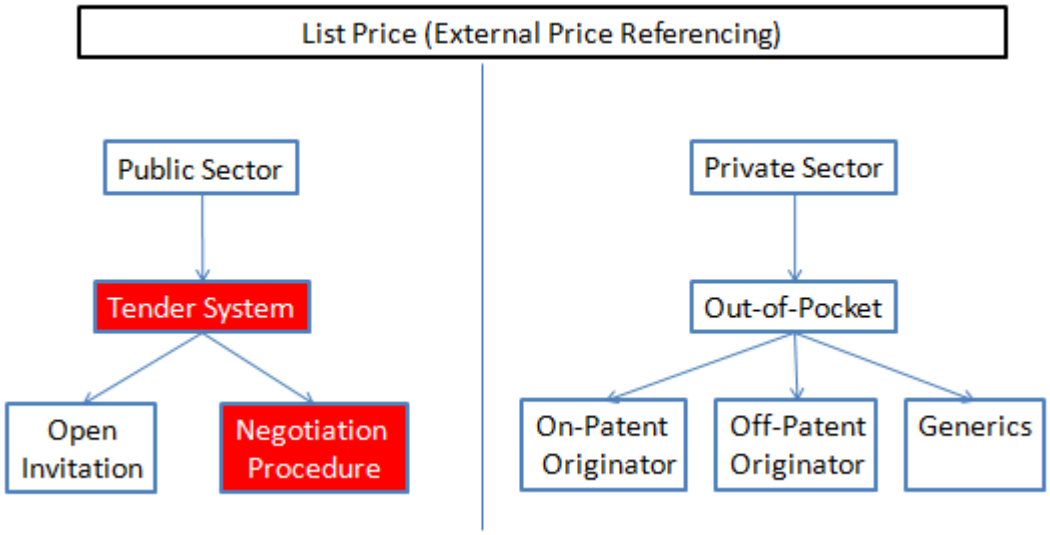
The negotiation procedure is reserved for new, on-patent medicines that do not have an alternative competitor at molecular level (but may do so at therapeutic class level). As explained in the previous section, the competent authorities (Dept of Pharmaceutical Services, MoH) invite manufacturers to agree on a price based on a projected volume, which guarantees the market for a given molecule. The regulatory framework is very explicit on the timing of this process and gives one calendar month to both parties to conclude a negotiation. Volumes are always fixed ex-ante and the terms that may be subject to some negotiation are (a) the number of deliveries (in instalments), (b) the shelf life of the product and (c) the timing of delivery. These procedures are mandated by the Accountant General to ensure that the process is transparent. The outcome of this process is made publicly available in the official gazette.

Our review of the current arrangements suggests that the share of on-patent originators in the public sector is nearly 50% of total public sector outlay on pharmaceuticals, of which expensive niche products are a substantial component (in excess of 50%). For on-patent products, the discounts achieved are usually between 5-10% off the list price, especially for oncology drugs, blood products, and monoclonal antibodies.

Several supply-side options are possible in the public sector system. Currently, manufacturers are reluctant to provide further discounts because the outcome of the negotiation process is made publicly available online on the government's e-procurement website. This can lead to spillover effects in foreign jurisdictions that reference the Cypriot drug prices. Our view is that the negotiation procedure and the existing legal framework around it potentially offer a unique opportunity for significant savings for the public sector by negotiating higher discounts. However, it would require agreements between the manufacturer and the competent authority to remain confidential. This is already the case in many EU member states, where confidential financial agreements (e.g. price-volume agreements, discounts, etc) and outcomes-

based agreements (e.g. outcome guarantees, coverage with evidence development, etc) are used to reduce financial risk and outcome uncertainty for payers; these agreements ensure that manufacturers have market access and that patients have access to potentially important and effective drugs. These arrangements are known as managed entry agreements (MEAs) or risk-sharing agreements (RSAs) (Ferrario and Kanavos, 2013). We would strongly support that the MoH leverage these policies in the Cypriot context.

Box 3. The negotiation procedure in the public pharmaceutical market segment



Recommendation 2

It is recommended that the Cypriot competent authorities price negotiate with manufacturers on the basis of risk-sharing agreements (predominantly price-volume agreements or straight discounts), which will be confidential in nature and will only be subject to statutory disclosures to government bodies for oversight purposes (e.g. General Accounting Office and Audit General). Currently, the legal framework does not allow direct and confidential negotiations to take place with economic operators on the basis of risk-sharing agreements, but it is recommended that the MoH/Pharmaceutical Services explore the feasibility of proposing such a framework as a matter of priority.

5.3. The supply-side: Options that will impact the public and private sector prices

5.3.1. Wealth adjustment to prices derived through EPR

Between 2005 (introduction of EPR) and 2009, Cyprus's GDP per capita continued to converge with the average GDP per capita (at international $) of the basket countries in the EPR system (Table 8). As a result of the recent global economic recession, however, the income per capita in Cyprus has declined by 8.5% between 2009 and 2012 relative to the average per capita income in the basket countries. Based on purchasing power parities (PPPs), the Department of Pharmaceutical Services could compare the GDP per capita in Cyprus with the average GDP per capita level in the basket countries and implement a correction to take into account the recent decline in per capita (and household) incomes.

The relative income level in Cyprus will provide the government with a concrete bargaining stance that will have significant impact in the private market to lower prices and alleviate the out-of-pocket burden on patients. This price discount will be self-controlled: if the economic conditions in Cyprus continue to deteriorate, the prices will continue to decrease, and vice versa. The rationale for this rebate is that prices need to decrease in the private sector given that the purchasing power of the average consumer has diminished. As the economic situation improves and the economy grows, the "wealth correction" will dissipate and eventually disappear.

The government has discretion over a few parameters: (a) when to implement this correction (e.g. implement in 2014 based on the latest available prices or implement in January 2015, once the forthcoming re-pricing in mid-2014 has taken place); (b) the size of the wealth adjustment, which is likely to be different taking 2012 or 2013 GDP per capita figures; and (b) whether to continue excluding products that cost less than €10 and which are predominantly off-patent drugs or generics.

A wealth adjustment, assuming it is modest-to-moderate, is likely the most politically feasible solution. However, the government should announce that this is a temporary measure, which will dissipate as the economy returns to growth and the current decline relative to the average income across the four basket countries reverses itself. This will ensure stability as the current system will continue to operate without any meaningful changes.

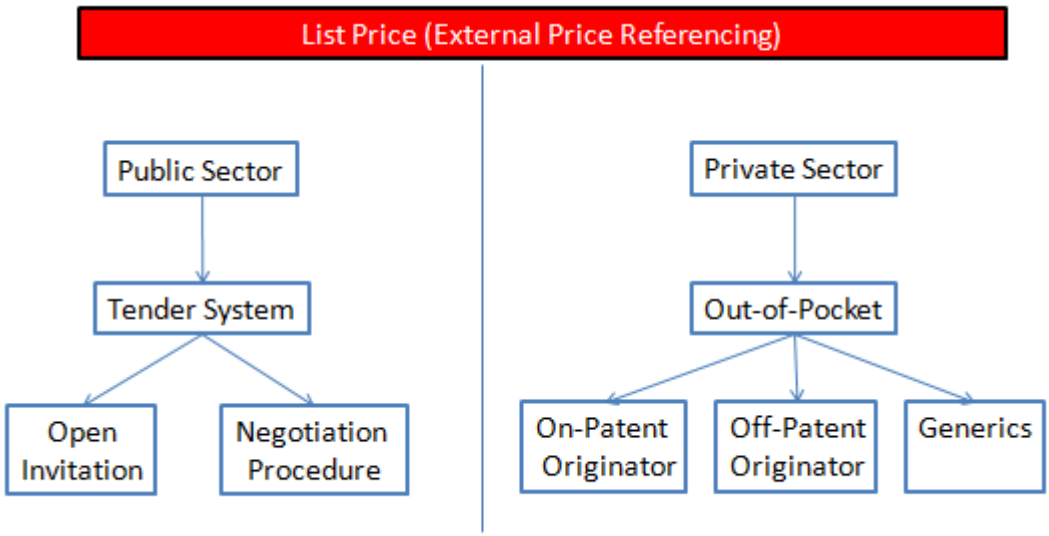
Table 8. Gross domestic product per capita, PPP (current international $)

Country	2005	2006	2007	2008	2009	2010	2011	2012
Austria	33,626.4	36,615.3	38,022.6	39,782.9	39,263.4	40,396.5	42,887.7	44,122.0
France	29,452.5	31,342.9	32,980.0	34,040.7	33,982.1	34,760.0	36,248.0	36,784.8
Greece	24,348.4	26,792.0	27,720.6	29,603.7	29,474.9	27,998.8	27,045.6	26,040.8
Sweden	32,703.0	35,736.1	38,426.1	39,615.0	37,606.7	39,568.6	41,762.7	42,865.8

Avg.	30,032.6	32,621.6	34,287.3	35,760.6	35,081.8	35,681.0	36,986.0	37,453.4
Cyprus	24,408.1	26,349.7	28,462.4	31,815.7	31,798.3	31,093.3	31,229.3	30,768.3
% difference between basket average and Cyprus	81.27%	80.77%	83.01%	88.97%	90.64%	87.14%	84.44%	82.15%

Source: All data from the World Bank.

Box 4. A wealth adjustment to prices derived through EPR



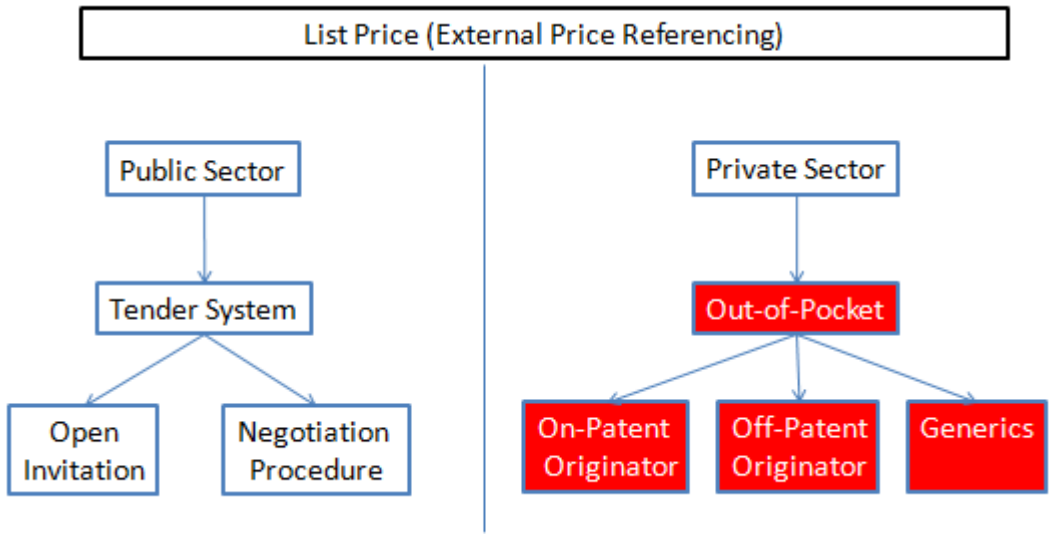
Recommendation 3a (Preferred option)

Introduce a wealth adjustment to the average prices derived from the existing basket (based on GDP differences between Cyprus and the current basket of countries). Based on the decline in GDP per capita in Cyprus between 2009 and 2012, the level of correction would be 8.5%. If it is implemented in 2014, it will have an immediate impact on prices at pharmacy level in the private sector and, therefore, on patient out-of-pocket expenses. Products priced less than €10 should be excluded. The public sector will only benefit if the starting point for the negotiation of new tender contracts is a lower price base. The government should review the wealth adjustment annually and adjust prices upwards or downwards accordingly.

5.3.2. Across-the-board price cut

An across-the-board price cut will have the same effect as a wealth adjustment and will have an impact on products in the private and public sectors. In the public sector, it will affect drugs for which an open invitation is in progress, rather than products for which there is a contract in place (prices cannot be changed after a contract is established). Despite the wealth adjustment and the price cut having the same effect (i.e. a downward pressure on the list prices determined through EPR), an aggressive price cut may have an impact on availability of certain products on the market if their prices are referenced by other countries.

Box 5. An across-the-board price cut that will affect prices in both sectors



Recommendation 3b (Second most preferred option)

Implement a modest-to-moderate across-the-board price cut in the region of 8.0-8.5%, but ensure that this will not have a deleterious impact on the availability of products whose prices are referenced by other countries.

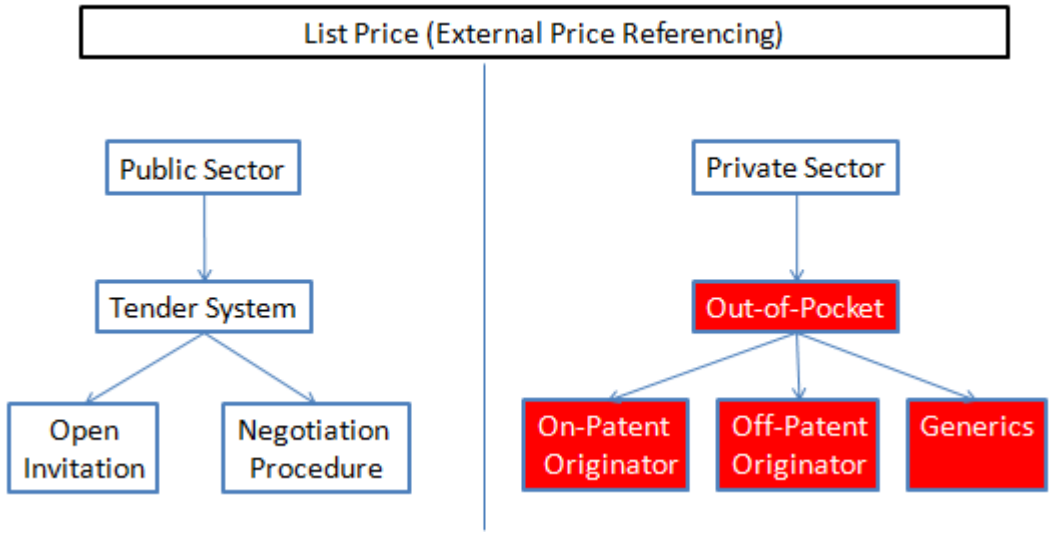
5.3.3. Introduction of a price decrease for off-patent drugs after their loss of exclusivity

According to existing regulation, originator brands whose patents have expired and are, therefore, subject to generic competition, are still priced based on the EPR rules that apply to new originator brands entering the market. It is, however, unlikely that patent expiry and the ensuing generic competition have any measurable impact on prices of off-patent originators, particularly in the private sector. This is due to the absence of any demand-side policies and the fact that the private market is predominantly a cash market (i.e. there is no protection through private insurance arrangements, purchasing

policies, generic prescribing, or generic substitution policies). In all other EU member states, compulsory INN prescribing and/or generic substitution are enforced, among other policies. Some EU member states, particularly those with weaker demand-side policies (for example, Greece and Spain) apply an across-the-board price reduction on the EPR-derived list price for reimbursement purposes. In Greece, once the originator patent expires, the price of the originator brand declines to 50% of its pre-patent expiry price. In Spain, the originator brand sustains a 40% price decline if it is to be included in a reference cluster with its generics and, therefore, continue to be reimbursed by the health care system.

In safeguarding the public interest, and considering that (a) off-patent originator pharmaceuticals have already capitalised on their market exclusivity due to patent status (plus supplementary patent certificates), and (b) the inability in the current setting to implement strong demand-side measures in Cyprus, it is proposed that the MoH implement a modest-to-moderate price reduction to the prices calculated through EPR prices for off-patent originator brands. The price cut should not be too substantial in order to ensure the continued supply of product on the Cypriot market and/or the discounts received in the public sector for these products. At the same time, the prices of the generic versions should continue being linked to the new originator brand at 80% of the originator price.

Box 6. An across the board price cut for off-patent originator drugs only



Recommendation 3c (Third most preferred option)

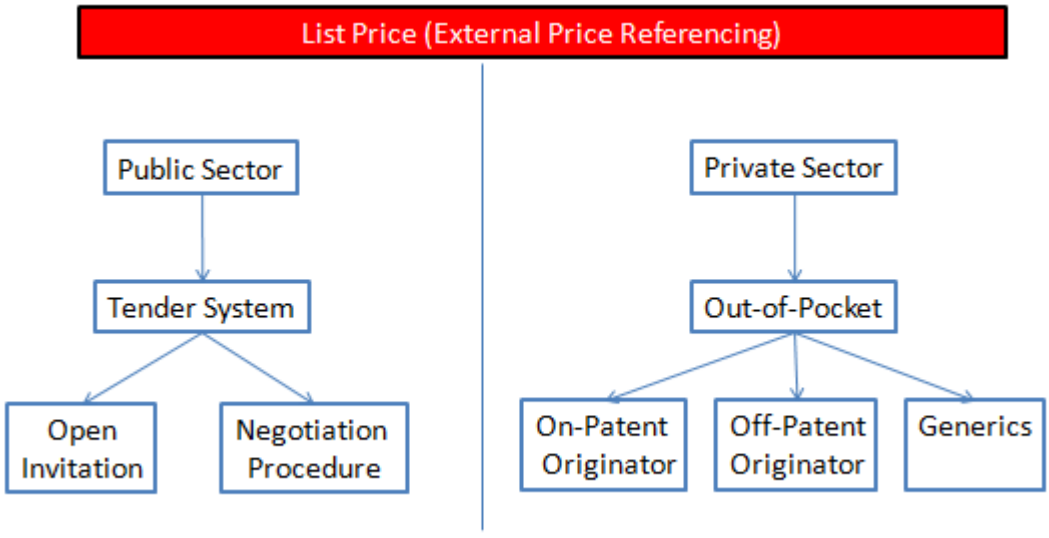
The MoH could implement a moderate price reduction to all off-patent originator brands, which will provide savings to private sector patients paying out-of-pocket. This price reduction should be between 20-30% to ensure adequate supply in the public

sector. Generic versions of the off-patent originator brands should continue to be priced at 80% of the originator prices.

5.3.4. Change the makeup of the EPR basket countries

A re-calibration of the pricing method and makeup of the country basket in the EPR system could deliver a reduction in list prices. For example, by moving from the average price in the existing basket of countries to the median or the lowest there will be a price reduction. In the lowest price is used, the price in Cyprus will be the Greek price, which is currently (one of) the lowest in Europe. Alternatively, the MoH could alter the composition of the basket (e.g. include the prices in two low-price countries and one medium-price country), which could lead to a modest-to-moderate price reduction. A careful simulation needs to be performed in either case, however, to understand the likely the likely market impact (e.g. availability). A decline in list prices will affect both the public and the private sector, but it is highly unlikely that it will result in savings for the public sector. As there is some overlap in the products offered on both markets, manufactures are likely to want to balance out a price decline in the private sector by offering higher prices in the public sector.

Box 7. A re-calibration of the reference basket to arrive at lower prices through EPR



Recommendation 3d (Fourth most preferred option)

Consider switching from the average to the median or the lowest price in the basket. Alternatively, consider altering the makeup of the basket, for example by taking two low-price countries and one medium-price country. However, a price decline in excess

of 8-10% may have adverse consequences (in terms of price and availability) for both the private and the public sectors and needs to be studied carefully before any reform is introduced. Re-calibration of the EPR system can have long-term effects.

5.4. Other interventions related to the pricing system

5.4.1. Frequency of price revisions

Price revisions are performed biannually except for new products. The prices of new pharmaceutical products are revised annually for the first two years. Thereafter, new products are re-priced once every two years. While the system is administratively simple, the government likely does not benefit from lower prices in the basket countries, or capture the effect of a patent expiry or loss of exclusivity in some cases. It is therefore recommended that annual price revisions are carried out. This is compatible with international practice, where price revisions are, in several cases, even more frequent (biennial or quarterly) (Kanavos et al, 2011).

For on-patent originator products, the Cyprus Association of Research and Development Pharmaceutical Companies (KEFEA) estimated that private sector spending will decline by 5% following the next price revisions that will be calculated mid-2014 and enforced on January 1, 2015 (see section 3.3).

Box 8. Annual price revisions

Recommendation 4

It is recommended that price revisions/re-pricing take place annually for all products. It is unlikely that additional capacity will be needed to implement this recommendation and the competent authorities will be able to capitalise sooner on price revisions taking place in the basket countries.

For the re-pricing that is intended to take place in mid-2014 (and will be implemented in January 2015), it is proposed that it goes ahead as planned. Downward adjustments will be made to prices according to which option will be selected from Recommendations 3a-3d.

5.5.2. Rebate in 2014 based on 2013 sales

For the drugs that are tendered in the public sector, it is not possible to adjust the existing prices, as these are irrevocable in accordance with national legislation. Given

the current economic climate in Cyprus, however, it is suggested that the government implement a one-off "good will" or "responsibility" levy from importers/manufacturers of originator products to alleviate the fiscal pressure on the national budget in 2014, assuming that other proposed pricing policies will take effect in 2015. This rebate is reasonable and justifiable considering the substantial decrease in the purchasing power of the average Cypriot patient and the reduction in the national budget for pharmaceuticals. The rebate would apply to contracts that have been concluded with the government.

Manufacturer rebates could be commensurate to their market share in the country (see *Table 9 in the appendix* for manufacturers with over €1 million in sales). This could form the basis of a broader transition towards more effective negotiations, through which the Cypriot government should be able to achieve substantial discounts. The structure of the rebate could be on a sliding (regressive) scale and would on average be in the region of 4-5%.

Table 9. Sales by manufacturer in the public sector (2013)*

(Appendix)

Box 9. A rebate based on 2013 sales to the public sector

Recommendation 5

In 2014, the MoH could implement a one-off rebate based on 2013 sales to the public sector, according to the market shares of various manufacturers (i.e. sliding scale). The average discount would be in the region of 4-5%.

5.5. Other supply-side interventions not related to the pricing system

5.5.1. Establish controls on pharmaceutical advertising

A number of regulatory interventions have been introduced over time to regulate the advertising activities of pharmaceutical manufacturers. First, direct to consumer advertisement (DTCA) of prescription drugs is prohibited by law across the EU. In addition, most EU member states apply legal provisions to control and monitor the promotion of prescription and OTC medicines. In general, limits on promotional activities apply; notably, free samples/give-aways and gifts are allowed, but are carefully monitored and regulated. Part of physician's participation at conferences can

be sponsored, but strict rules apply in most countries about the amplitude of such sponsorship. The institutions responsible for the regulation and monitoring of medicine advertising include governments, MoHs, as well as self-regulation (codes of practice that are adhered to) from medical societies and pharmaceutical industry associations.

In addition to action by EU member states, national industry codes of conduct on advertisement and promotion are complementary instruments to control advertising activity. Adherence to the code of conduct is voluntary, but most codes contain formal procedures for complaints and sanctions.

Overall, from a government regulation perspective, a number of facets of company advertising activity are subject to control or intervention, as follows:

- Limits on promotional activities (e.g. as a percent of total sales);
- Increased taxes for advertising activities (e.g. as a percent of total sales);
- Restrictions on the number of free samples provided to physicians and other health care professionals;
- Restrictions on the provision of promotional material to physicians and other health care professionals; and
- Restrictions on physician and other health care professional entertainment as well as funding for participation in conferences (e.g. conference registration fees, as well as travel and accommodation expenses)

Box 10. Pharmaceutical advertising controls.

Recommendation 6

The MoH should introduce legislation to establish limits on all forms of pharmaceutical advertising by manufacturers and their representatives. The MoH should also ask manufacturers, their representatives, and the medical profession to put together appropriate codes of practice for this purpose. Consequently, the MoH should attempt to fill the gap in the provision of information on pharmaceutical products to stakeholders.

5.5.2. Re-define the role and constitution of the pricing committee

Most EU member states rely on a pricing committee to inform pricing decisions for on-patent and off-patent medicinal products. All EU countries have implemented steps and procedures to safeguard the objectivity, transparency, and timeliness of the committee

procedures to ensure that any decision is defensible to all relevant stakeholders. In Cyprus, however, the Pricing Committee that recommends list prices to the Minister of Health currently consists of a number of public and private stakeholders. Notably, the importers, patient groups, the Pancyprian Pharmaceutical Association, local manufacturers and research-based manufacturers are all represented in the Committee and are allowed to vote on actions that influence the domestic prices. The committee should only consist of technocrats, bureaucrats, academics, and institutional stakeholders with the relevant skills, including pharmacy, medicine, health economics, and law. It is essential to exclude individuals with conflict of interests. It is recommended that Ministry of Health solicit the opinions of these groups and grant them the right to appeal any decision without being directly involved in the process.

Box 11. Re-define the role and constitution of the pricing committee

Recommendation 7

The ultimate goal of the pricing committee is to validate the results of the pricing formula and recommend products in question to the minister of health based on scientific and pricing information. The pricing committee membership should include institutional stakeholders (medicines regulatory body and MoH) and scientific personnel only.

In the context of reimbursement and once a system of reimbursement has been introduced, additional stakeholders (e.g. patients and industry) may participate in meetings, or have the right to submit evidence, but would not have voting rights.

5.6. The demand-side: Options for prescribing, dispensing and cost-sharing

5.6.1. Prescribing guidance for the public sector

No provisions exist to check whether drugs used appropriately. The extent of clinical practice guidance is unclear in both the private and public sectors. In the short-term a number of prescribing guidelines can be developed for high-cost and/or high-volume therapeutic classes. Prescribing guidance should provide precise direction to physicians based on the principles of clinical cost-effectiveness.

As many EU member states have already implemented such guidelines for the vast majority of therapeutic indications, a suitable first step would be to adapt the available evidence and practices to the Cypriot context. This would be time- and cost-effective. A selection of prescribing guidelines could be piloted in the public sector and should be binding for practising or contracted physicians. For the medium- and the long-term,

there is urgent need to compile prescribing guidance for all conditions and to enforce them amongst practising clinicians. This will be particularly beneficial following GeSY implementation.

Box 12. Prescribing guidance in the public sector

Recommendation 8

It is recommended that for medicines prescribed in the public sector, the government pilots prescribing guidance in a small number of disease areas/conditions to rationalise use; this should improve quality of care and optimise spending. This could be done for a number of high-cost conditions, such as hypertension, dis-lipidaemia, and osteoporosis. This will enable the authorities to place individual drugs in the context of the disease and its treatment, as well as outline treatment options and their sequence and duration.

5.6.2. Tenders conducted at therapeutic class level

Tenders for out-patient pharmaceuticals can drive prices down significantly and, if sustained over successive tender cycles, can result in substantial savings, whilst at the same time they can optimise prescribing in therapeutic areas, where significant options exist. The submission of the tender implies that discounting practices at retail level are eliminated, and that, on aggregate, purchasers are in complete control of the procurement process. Some of the stakeholders may be affected either because of greater logistics spending and discount elimination (i.e. pharmacists), or because of the requirement to explain to patients any change in the drug prescribed (i.e. pharmacists and physician). There may also be some confusion among patients if changes are observed (e.g. colour, shape, size, etc.) to the preferred drug(s) after subsequent tenders. In order to ensure that adherence is not affected, pharmacies need to play a key role in advising patients of such changes to their drug regimens.

Cyprus has had considerable success implementing the open invitation procedure for over two decades, especially for off-patent products. However, two modifications to the current system are proposed, which aim to improve efficiency and potentially increase savings over the medium-term. The first relates to the concept of therapeutic class level tendering: grouping either all versions of the same molecule (ATC-5 level), or all molecules in a tightly defined product category (ATC-4 level) and requesting bids across the molecule or the product class. The latter can be achieved in circumstances where there is wide evidence on the inter-changeability amongst the options available (e.g. PPIs, statins, ACE-I inhibitors, beta-blockers, and CA-channel antagonists). The second relates to the number of successful bids. In the current system, the lowest bid is accepted and that manufacturer gets to supply the whole market. Several other countries that use tendering, however, award contracts to more than one manufacturer

to ensure that competition is sustainable in the long-term. In Germany, for example, there can be up to three manufacturers that are allowed to supply the market, the latter being defined regionally.

We recommend that both options (wider groups for tenders, including therapeutic class tenders, and multiple winners), should be investigated by the Cyprus competent authorities to determine the scope of introducing changes to the legal framework over the short term.

Box 13. Tendering (open invitation) at therapeutic class level

Recommendation 9

It is recommended that for medicines that can be grouped into inter-changeable therapeutic clusters, tenders at therapeutic class level (e.g. across all statins 10mg or ACE I inhibitors) be conducted. This could take place as a pilot and contracts could be awarded to the two or three lowest bids from across the therapeutic class. The legislative implications need to be explored first before proceeding (e.g. if the current framework only allows the lowest price to be awarded the contract).

5.6.3. Improving the perception of generic medicines

It is essential to improve patient perceptions of generic drugs. In Cyprus, the patient advocacy group noted that many patients do not perceive generics as bioequivalent to the originator product. It is therefore important to introduce an information campaign targeted at patients. Such a campaign should educate patients about the cost-saving potential of generics, which is important for the sustainability of the health system. The government (MoH), or another objective information source, should carry out this campaign to hopefully shift consumption habits over the longer term from more expensive brands to cheaper generics. The government should also launch a promotion campaign to explain the concept of bioequivalence to patients to ease their safety and efficacy concerns and illustrate why generic drugs can be priced much lower than originator drugs. A common fear among patients is that the low price of a generic is indicative of low quality, analogous to the low price of a knock-off brand of clothing. Patients must realise that the generic manufacturers do not incur the same sunk R&D and advertising costs, resulting in substantially lower prices.

Box 14. A campaign undertaken by MoH to improve the perception of generic medicines

Recommendation 10

Improving the perception of generic medicines among prescribers and the general public is essential. The MoH could undertake an information campaign about the value and quality of generic medicines in Cyprus and their inter-changeability (bio-equivalence) to brands; this should deliver results in the longer term.

5.6.4. Remuneration of retail pharmacies

It may be necessary in the current round of reforms of the pricing system to re-visit the system of pharmacy remuneration.

According to data provided by the Pharmaceutical Services, 81.3% of sales in the private sector, in 2013 (that is €110.5 million), concerns medicines for which their wholesale price is below €50. Based on current practices, these medicines fall into the broad category of the 37% retail markup added to the wholesale price. This is one of the highest allowable markups in EU Member States and merits revision. Such a revision would include (a) a reduction to the maximum retail markup to levels closer to those prevailing in EU Member States, (b) an increase in the number of regressive scales at appropriate price ranges and (c) eventually, a disconnect of the income of pharmacists from the pricing of medicines post-implementation of the National Health Insurance Scheme. The timing of all the above can be flexible and needs careful consideration, in line with health insurance reform implementation, perhaps with the exception of the maximum markup (point (a) above), which could be addressed as a matter of priority.

Box 15. Re-visit the upper ceiling of pharmacy remuneration with a view to rationalising it downwards and ultimately disconnect pharmacy income from medicines' pricing

Recommendation 11

It is recommended to reduce the maximum retail remuneration ceiling in line with levels currently prevailing in the rest of the EU. Overall, it may be necessary to re-visit the overall remuneration structure of retail pharmacy with the addition of regressive mark-ups at appropriate price ranges and, eventually, a disconnect of pharmacy income from medicines' pricing.

6. Reforms over the medium term: A roadmap for the introduction of the Generalised Health Insurance scheme (GeSY)

In the mid-term, the key objective will be to prepare the country for a smooth and efficient transition to the national health insurance scheme. During our visit, we were explained that much of the broad thinking and principles around reimbursement has taken place; however, the detail of how to implement a national pharmaceutical policy in the context of the proposed generalised health insurance scheme (GeSY), as well as the prior actions required for this purpose (e.g. simulations, pilot studies, and legislation), are not yet established.

For the pharmaceutical sector, it will be important to decide on several supply- and demand-side issues, run a number of pilots and/or simulations prior to the introduction of health insurance to ensure that the options considered are optimal and will not result in expenditure over-runs or other unforeseen issues, and, finally, draft and pass any necessary legislation. This will require close contact and collaboration between MoH and HIO to leverage skills, experience, and expertise. The two groups should jointly outline the rules, roles, and responsibilities of each and engage in preparatory work together to ensure the sustainability of the system after health insurance implementation.

The sections below outline actions on the supply- and demand-side and a roadmap for the next 3-4 years in preparation for health insurance implementation. It will be a time-consuming process that includes drafting, amending, and passing legislation. These should be addressed with immediate effect to enable the successful and smooth transition to a national pharmaceutical policy under generalised health insurance.

6.1. Pricing

Some adjustments to the existing pricing system may be required prior to the introduction of national health insurance. Assuming a separation between pricing and reimbursement, it is not recommended to undertake fundamental changes to the current system of pricing if the reimbursement assumes a central role in determining cost-effective prices (and use) to ensure efficient resource allocation. The current pricing system guarantees relatively high prices to originator manufacturers (for both in- and off-patent drugs) and to generic manufacturers (prices as a high proportion of the branded price). Some incremental changes could be considered as follows:

- First, current EPR prices could be reduced through a wealth adjustment, as discussed in the previous section. This would be the preferred policy option and would not require changes to the basket of countries or re-calibration of prices (e.g. moving from the average in the basket to the lowest, or adding a second low-price country in the basket).

- Second, price revisions could easily take place annually, instead of once every two years, to capitalise on price reductions in the basket countries.
- Third, the pricing committee membership will need to be altered to only include institutional stakeholders (Medicines Agency and MoH), as its remit is to validate prices arrived at through the EPR system. However, the committee rules should allow relevant stakeholders to review draft decisions and, if necessary, appeal.

6.2. Reimbursement

Currently, Cyprus does not have a reimbursement system: all public-sector drugs are covered fully and with no co-payment. The establishment of GeSY will require appropriate reimbursement policies, the precise details of which need to be worked out prior to the introduction of generalised health insurance, as outlined in the next three sections.

6.2.1. Principles of reimbursement

The reimbursement policy should be characterised by a number of principles. These form the operating framework and are usually enshrined into legislation. Key principles include:

- **Transparency**. The processes need to be clearly outlined and specific timelines need to be observed by stakeholders.
- **Flexibility**. New treatments are made available to patients within a reasonable amount of time.
- **Robustness**. Validated processes need to be in place to evaluate clinical benefit and assess the economic impact of the treatment.
- **Stakeholder input**. A good reimbursement policy should encompass views from all stakeholders.
- **Comprehensive coverage**. This needs to be guaranteed for all patients at a reasonable cost and by reducing the out-of-pocket burden significantly. If 80% of the market is covered under the current system on a 100% basis (i.e. zero co-payment), it will be difficult to convince stakeholders that co-payments will be necessary to ensure stability and sustainability. Such co-payments will need to be designed a-new.
- **Choice**. A reimbursement system needs to maintain adequate choice, but not at the expense of significant out-of-pocket expenditure.

- **Rational drug use**. It implies greater use of generics and their acceptance by both the medical profession and the patient community.

6.2.2. Key tools guiding reimbursement on the supply-side

The following work streams are envisaged on the supply-side:

First, the **establishment of a national positive list or formulary**, in line with standard practice across all insurance-based systems; the formulary will contain the out-and in-patient medicines that health insurance will reimburse, as well as their rate of reimbursement (i.e. level of cost-sharing). A number of preparatory steps need to be undertaken, as follows:

1. **Forming a single list under health insurance**. There has to be agreement over how to fuse the drugs available in the public and private sectors into a single, coherent tool that will include all drugs that health insurance will cover.
2. **Reimbursement committee.** There needs to be an executive body that will administer and have oversight over the positive list implementation. This committee will decide on which drugs are included in the positive list and the selection criteria for including new drugs (and procedures for de-listing). An agreement needs to be reached about who participates in this committee (e.g. number of seats, stakeholder participation), who chairs it, what are the terms of reference for the key members (e.g. their background and expertise), and what background support does this committee need (e.g. a secretariat). In addition, there may be a need for capacity building for certain tasks, such as establishing the criteria for the admission of new drugs into the positive list. Finally, procedures need to be established, based on EU norms (e.g. the Transparency Directive), regarding the timelines for negotiations, frequency of committee meetings, stakeholder involvement, and appeals processes, among other features.
3. **Criteria for admission of new drugs into the positive list and criteria for de-listing**. There needs to be agreement on the criteria that will allow drugs to enter the positive list (or be de-listed). Criteria and procedures need to be established for drugs in both new and existing indications. For these drugs, it will be important to determine how 'value' will be measured and what role clinical and (socio-) economic criteria will play. Criteria and procedures will also need to be established for the reimbursement of off-patent medicines (e.g. internal reference pricing); it will also be important to clarify the role of tendering in the new system. Finally, a framework needs to be established for OTC medications, which

the health system will not reimburse; this would include guidance on when to switch certain compounds from prescription only (POM) to OTC.

4. **Process management and legislative interventions**. It is very likely that all of the above steps will require (a) significant background work and agreement among all relevant stakeholders and (b) legislative interventions. A working party of experts from the relevant stakeholders and competent authorities will undertake this task, perhaps with the participation of outside experts, with a view to preparing the relevant documentation and draft legislation. The time required for this is likely to be a minimum of 9-12 months.

Second, as part of the work stream on defining reimbursement, there needs to be specific focus and a set of decisions on what is the **value of new medicines**, how it should be assessed, and what provisions need to be made for the reimbursement of new drugs that come on the Cypriot market. In this context, the following parameters will be of interest:

1. **Role of economic criteria**. Although the size of the country does not justify the establishment of an arms-length body to perform its own independent health technology appraisals, economic criteria (coupled with clinical evidence) should guide decision-making. The process of HTA adaptation (particularly as concerns costs) could be driven by manufacturers and would be based on guidelines issued by the competent authorities. Additional evidence on clinical and cost-effectiveness could be taken into consideration from a wide variety of HTA bodies in Europe (e.g. NICE, SMC, TLV, HAS, IQWiG) and elsewhere (e.g. PBAC, CADTH) that have the appropriate resources. This would require some capacity building at the local level to equip individuals with the expertise needed to evaluate economic evidence and incorporate it into decision-making.
2. **Role of risk-sharing and managed entry agreements**. An increasing number of therapies for rare conditions and niche markets are subjected to financial and/or outcomes-based managed entry arrangements in view of their high cost and outcomes uncertainty. Local decision-makers will need to embrace these tools, as they can potentially lead to significant savings for health insurance. The appropriate regulatory (and legal) framework will need to be put in place defining what these arrangements will be and who will have responsibility for negotiations and who will have the ultimate oversight.
3. **Capacity building in economic evaluation, risk-sharing and negotiation principles**. It will be necessary to incrementally build capacity and expertise on a sustainable basis on a number of critical skills:

economic evaluation and modelling, risk-sharing agreements, and negotiation skills. While some of this expertise already is present in the competent authorities, these needs and the number of individuals to be trained should be identified early; training of the relevant individuals should be completed before the implementation of health insurance.

4. **Process management and legislative interventions**. All the above will require detailed preparation and agreement among the competent authorities. A legislative intervention may also be required with regard to all aspects of economic evidence use and risk-sharing arrangements.

Third, a method of reimbursement for off-patent drugs needs to be introduced. Specifically, the roles of **internal reference pricing** and **tenders** for off-patent drugs need to be explored and piloted.

1. **Internal reference pricing (IRP)**. IRP is used extensively in most EU countries and elsewhere to determine reimbursement when drug patents have expired and generics are available. An IRP system can include both molecular as well as therapeutic referencing. Simulations can take place to determine the likely impact of therapeutic reference pricing based on current data across a range of drug categories. Provisions will also need to be made if competition through IRP does not deliver significant cost savings to health insurance (e.g. exploring scenarios of managed competition for molecules with large market size). Simulations can take place prior to health insurance implementation, as actual data for this purpose are not yet available.

2. **Tendering (open invitation process)**. The Cypriot authorities have accumulated considerable experience in the use and administration of tenders through the current open invitation process. A precise regulatory/legislative framework exists that is compatible with EU legislation. This expertise needs to be preserved and be used for both in- and out-patient drugs. Tenders could be seen as an additional tool in out-patient markets to select cost-effective choices (e.g. if internal reference pricing does not deliver significant savings), even if this means restricting formulary choices. The competent authorities can start to identify potential drug targets before the implementation of health insurance (e.g. when competition is limited and when a tender approach might deliver better results for health insurance than alternative reimbursement methods).

- Within the context of reimbursement, the competent authorities need to define the role of **other reimbursement tools**, such as **portfolio management**. It might be possible to use current data and evidence to simulate the likely benefits

for health insurance and the general health system of using such tools. Assuming that any provisional evidence is positive regarding their use, it may also be necessary to introduce their scope into legislation, as well as train staff in their use.

6.2.3. Key tools guiding reimbursement on the demand-side

The following work streams are envisaged on the demand-side (proxy demand-side if it targets physicians or pharmacists):

First, as health insurance becomes operational, it will also have control over **prescribing**. A number of actions need to take taken and the arrangements for these to be finalised prior to health insurance implementation. Key actions include:

1. **Health service delivery: primary and secondary health care**. Assuming a primary-care model, all physicians need to be contracted in advance. Contractual arrangements need to be outlined in detail and physicians need to be aware of (and agree to) their role in an environment of universal coverage by health insurance.
2. **Physician remuneration and incentives to ensure quality of care and rational drug use**. Decisions will need to be made about methods of physician remuneration (and the budget impact) and the status of all physicians (e.g. primary care, secondary care) that are employed by or contracted through the health insurance system and the extent to which they will be able to practice in the private sector or the extent to which any private facilities will be contracted into the public system.
3. **Information technology and electronic prescribing**. The cornerstone of an effective prescribing system is an electronic prescribing system (e-Rx), through which physicians will have access to clinical and drug information. In addition, the link between insurance, prescribing, and dispensing is safeguarded through the use of an effective information system, whereby connections can be made between diagnosis, prescribing, dispensing, and overall utilisation. The establishment of such a system is timely as it requires an initial investment through procurement mechanisms and software that will probably need to be calibrated to local circumstances over time. The system should be piloted prior to nationwide rollout.
4. **Prescribing guidance**. Prescribing guidance needs to be available and be incorporated into the electronic prescribing system. This will enable physicians to prescribe in accordance with evidence-based medicine, while at the same time subscribing to certain rules set by health insurance

(e.g. INN prescribing). Whereas such guidance is readily available from many settings, its selection and adaptation may take some time, as it will require a degree of consensus to be achieved among the medical profession and competent authorities. It would be good to pilot the preparation of prescribing guidance across the ten most costly conditions in Cyprus.

5. **INN prescribing, Rx monitoring, and audit**. Rules will need to be established about how physician prescribing will be monitored, the frequency of audit operations, and the sanctions for those who ignore prescribing guidance.

Second, a number of actions are required on **dispensing** prior to health insurance implementation.

1. **Determination of pharmacy remuneration method**. A suitable pharmacy remuneration method will need to be identified. A number of issues need to be addressed: (a) type of remuneration and whether it should be regressive or a flat fee; and (b) the level of proposed remuneration, including a minimum income level for pharmacies. These features should be determined with the understanding that the pharmacies will serve 100% of the patient population in the fused system, as opposed to the current 20% in the private sector. As the average pharmacy mark-up is now about 25% of the cost of medicines, it is important that these features are resolved before the implementation of generalised health insurance. Finally, assuming that some products (especially off-patent drugs) will continue to be tendered, the framework for pharmacy payments for those products delivered in primary care through community pharmacies will need to be clarified.
2. **Generic substitution**. Pharmacies need to be given rights to substitute generically. There are different "shades" of generic substitution, ranging from very restrictive (e.g. in emergencies only or with doctor's permission only, to mandatory generic substitution). The competent authorities will need to decide which option best serves the public interest.
3. **Other services supplied by pharmacists**. Decisions will need to be made about whether other services will be delivered by pharmacies and, if so, what the level of reimbursement for these services will be.

Third, a further set of decisions will have to be made on **patient cost-sharing**, which is related to the rules of pharmaceutical reimbursement. In particular, there are two broad questions that need to be addressed:

1. **Exemption criteria.** These are typically associated with one or more of the following parameters: (a) age, (b) income, or (c) type of disease. For instance, medicines for life-threatening conditions, such as diabetes or cancer, are usually excluded from the scope of cost-sharing.
2. **Type of cost-sharing.** Several options exist for statutory co-payments, including deductibles, co-insurance, and flat co-pays, as well as any combination of these. Differences between reference prices and the price of the drug of choice are also classed as co-payments. Decisions will need to be made about which classes of medicines will carry statutory co-payments, what their level will be, what is the target income expected from this source, what the likely impact will be on insurees, and how these will be levied.

Finally, it may be necessary to outline the details of all or some of these demand-side arrangements in legislation.

6.3. Summary of pharmaceutical policy actions to be undertaken in anticipation of GeSY implementation

The list below outlines a number of essential actions that need to be completed before the implementation of GeSY to ensure that (a) the legislative/institutional framework is up-to-date, (b) the competent authorities acquire time-sensitive knowledge of how the country is likely to operate in an environment of health insurance and (c) the competent authorities identify and address some of the gaps and teething problems that such a system will have prior to its rollout to the entire population. These actions can be part of a 3-4 year work programme. It would not be wise to implement GeSY before these take place.

- Re-calibrate the system of pricing and maintain its independence relative to the system of reimbursement; re-define the role and membership of the pricing committee and undertake all necessary legislative changes. Define management roles and implement price revisions annually.
- Establish a national positive list or formulary by fusing the treatment options currently available in the public and private sector.
- Establish a reimbursement committee and all the processes around it (e.g. headcount, membership, transitional arrangements, etc), including a secretariat that is in charge of the background work related to the inclusion of new medicines on the positive list (i.e. formulary).

- Establish the criteria for admission of new drugs into the positive list, as well as criteria for de-listing. Establish a framework for over-the-counter medicines and the switch of compounds from prescription-only to over-the-counter medicines.
- Decide on the precise role of economic evaluation in the decision-making process and how to operationalise such a system (including capacity-building).
- Decide on the tools required to enable the Competent Authority to negotiate successfully with manufacturers over new and expensive therapies (e.g. outcomes-based risk sharing, price volume agreements, etc); decide how to operationalise such negotiations and what capacity-building activities are needed.
- Introduce internal price referencing, which will encompass both molecular and therapeutic price referencing; define the therapeutic classes for which the latter can be implemented; simulate the impact on reimbursement across a range of therapeutic classes under conditions of health insurance for the entire market.
- Define the scope of tendering; identify likely targets for tendering and simulate the effect of tendering under conditions of a unified health insurance market across a number of products (e.g. on-patent, off-patent branded, and generic).
- Define the role of and scope for other reimbursement tools, such as portfolio management, and quantify their likely impact.
- Pilot the arrangements around primary health care (gate keeping), physician remuneration, and any incentives to improve quality of care prior to introduction of health insurance.
- Establish an electronic prescribing (e-Rx) system, which will require hardware, software, and pilot testing. If procured through open processes, as per EU directives, the time commitment can be significant. Once in place, it needs to be guaranteed it runs effectively by piloting it in one or two areas. As the process is onerous and subject to EU procurement rules, it may be wise to attempt to by-pass some of these restrictions by incorporating this task into the Memorandum of Understanding (MoU) targets as soon as possible.
- Conduct a pilot for the preparation of prescribing guidance for the ten most costly diagnoses/conditions in Cyprus.
- Link prescribing guidance to the e-Rx system and ensure that the system operates well.
- Pilot the implementation of e-Rx with prescribing guidance to determine physician compliance and expected savings.
- Simulations on cost of prescribing under the new conditions for the ten most expensive diagnoses/conditions at ATC-3 level under current circumstances;

also simulate the cost effect when prescribing guidance has been produced and it is linked to the e-Rx system.

- A detailed and comprehensive study on pharmacy remuneration given that they will serve the entire market after health insurance implementation. This should be based on a comprehensive and representative sample of the public and private sectors.
- Identify a suitable cost-sharing policy, including exemption criteria and type of cost-sharing that will not carry a disproportionate financial burden for patients and administrative burden for health insurance. Link cost-sharing to the positive list.
- New legislation or amendments to existing legislation will need to be produced for many of the above areas once the evidence has been produced and discussions have taken place between the relevant stakeholders. Draft legislation can be bundled into coherent groups each addressing a subject area. It is envisaged that amendments to existing laws or new legislation will need to be produced as follows:
    - Amendments to the Law on Human medicines (Quality Assurance, Procurement, Pricing)
    - Amendments to the Law on Pharmaceuticals and Poisons
    - Amendments to the Law on Psychotropic and Narcotic Substances
    - Amendments to the Law on National Health System
    - Establish legal framework to enable confidential negotiations with manufacturers
    - Establish legal framework for the reimbursement of pharmaceutical products, the establishment of a reimbursement committee, the positive list, the rules of remuneration and responsibilities of prescribers and pharmacists, and the co-payments by patients
    - Establish legal framework for INN prescribing and generic substitution
    - Establish legal framework for the contractual agreements between the medical profession and health insurance/the government.
- The roadmap will also include allocation of responsibilities and tasks among competent authorities to leverage the expertise developed to date.

7. Reforms over the long-term: Pharmaceutical policy in the context of health insurance implementation

In the long-term, it is important to consider policy options in the context of a newly implemented national health service. It is important to institute transparent, effective, and objective pricing and reimbursement systems that safeguard the affordability and availability of medicines for all patients, as well as the sustainability of the health care system.

7.1. The supply-side

On the supply-side, the most important development should be the move to a system of reimbursement. It will be important for the HIO and Department of Pharmaceutical Services at the Ministry of Health to establish the parameters of a reimbursement system and the levels of coverage, for example based on therapeutic indication. This should also include drug evaluation criteria, most likely under the auspices of a newly-formed reimbursement committee; the terms of reference and the criteria for admission into reimbursement will also need to be established.

Currently, Cyprus relies exclusively on pricing methodologies to control prices and contain pharmaceutical spending. All other EU member states rely on a mixture of pricing and reimbursement strategies, which offers much more flexibility and many more opportunities during negotiations with firms. In the mid- to long-term, the government should consider transitioning to a quasi-health technology assessment (HTA) system that considers cost-effectiveness evidence for on-patent products, instead of the current use of tendering.

For example, for on-patent products, the Cypriot government could rely on reimbursement to achieve confidential discounts by only reimbursing a certain proportion of the list price. The Ministry of Health could apply cost-effectiveness and willingness-to-pay parameters to guide the negotiations and drive manufacturers to lower prices to an affordable level. Although it is not logical for a small country like Cyprus to introduce an independent and fully-developed HTA body that generates its own data, the Ministry of Health could deploy a team comprising a few individuals with technical expertise in health economics who would monitor, collect, and analyse HTA evidence from other settings and produce recommendations for Cyprus based on these.

The government would then be equipped to demand manufacturers to submit cost-effectiveness information when requesting marketing authorisation in Cyprus. It is easy for firms to adapt their cost-effectiveness models to local circumstances (e.g. costs, burden of disease, etc.). The government can complement this information with published data from other HTA bodies in Europe, including the National Institute for

Health and Care Excellence (NICE) in the United Kingdom and the Dental and Pharmaceutical Benefits Agency (TLV) in Sweden. The evidence suggests that these strategies can optimise both prices and utilisation for on-patent products, even in small countries like Cyprus.

This will also enable the government to implement risk-sharing agreements in the long-term. Regulators increasingly promote risk-sharing agreements to hedge against the uncertainties regarding budget impact, clinical effectiveness, cost-effectiveness, and other relevant endpoints that remain at the time of market entry. In general terms, manufacturers are granted favourable pricing and coverage levels in return for achieving financial (e.g. price-volume agreement) or outcome targets (e.g. evidence development in clinical setting). The conditions of these agreements are usually set through confidential negotiations between manufacturers and competent authorities, which require a legal framework. Several types of risk-sharing agreements exist, including coverage with evidence development, conditional coverage, outcome guarantee, price-volume agreements, portfolio deals, and disease management.

The increased use of risk-sharing agreements over the past five years in many European countries, Australia, and Canada signals a departure from static price regulation. It marks the advent of an era of negotiation between competent authorities and manufacturers on the basis of the incremental value of novel medical technologies. Prices are negotiated based on financial or outcome agreements, and the agreement conditions are kept confidential. Despite their challenges and limitations in terms of implementation and performance measurement, risk sharing agreements provide a departure from EPR principles and render list prices in other countries irrelevant to policymakers.

For off-patent products, an internal reference pricing (IRP) could be implemented alongside the existing price cap, although the latter may need to be revised downwards in accordance with international norms. As previously explained, payers often use the lowest-priced generic in IRP schemes to set a maximum reimbursement level (i.e. reference price) for a particular product. A product whose price exceeds the reference price is either not reimbursed, or the patient has to pay the difference between the reference price and the actual price of the product out of pocket. The reference price is usually the lowest or the average of the lowest prices of the group. In some therapeutic classes, a reference price applies to a therapeutic class, rather than a single molecular group. This means that more products are included in the reference group, some of which may be still protected by patents. This is used to prevent expenditure on “me-too drugs,” or new drugs with very similar therapeutic effects to existing alternatives. As these drugs are on-patent, they are priced much higher than generics of other off-patent pharmaceuticals of the same therapeutic class. The evidence on what therapeutic classes can be included in reference clusters (and the impact of therapeutic IRP) is quite extensive and the competent authorities could build on this.

The aim of reference pricing is to contain third-party pharmaceutical expenditure (and indirectly the prices of specific products) and to encourage patients and physicians to consider costs when choosing between equivalent medicines. In other words, reference pricing seeks to increase competition by making demand more price elastic. If patients must pay the difference between the reference price and product price, there is a financial incentive to demand the cheaper option. The Cyprus Federations of Patients Associations have both expressed that they are in favour of an IRP system with cost sharing for patients who elect to continue to use originator products following patent expire. The role of the competent authorities in maintaining the public interest would be to encourage rational drug use by promoting the use of generic equivalents. In cases where IRP fails to stimulate competition, tendering may be an option.

7.2. The demand-side

On the demand-side, it will be important to enforce mandatory generic substitution and INN prescribing, as previously explained; these should have been implemented in the prior to the introduction of national health insurance. Most of the relevant changes should have been implemented in the short- and medium-term. An electronic prescribing system that is linked to prescribing guidance – perhaps the single most important policy intervention - should enable prescribing and drug use to be monitored effectively. It would also enable competent authorities to introduce prior authorisation principles for drugs that are particularly costly for the health care system. An important demand-side change under a national health insurance scheme will be the introduction of cost sharing for some drug classes to divide the cost burden between the health care system and patients. An appropriate cost-sharing policy will need to be implemented. Exemptions would be based on socioeconomic conditions (e.g. income, age, etc.) to protect vulnerable populations. The government can also consider alternative cost sharing arrangements (and cost sharing rates), including coinsurance, deductibles, and co-payments. As previously mentioned, the IRP system will result in patients paying the difference between the reference price and a higher drug price if the patient elects to not purchase the lowest-priced drug. Finally, an important consideration for Cypriot competent authorities would be the appropriate management of information to patients (e.g. about the bioequivalence of generics, etc.).

8. Conclusions

Given the rising costs of new drugs and limited national budgets, regulators strive to achieve a balance between ensuring affordable health care and enabling the use of innovative pharmaceuticals. National pricing and reimbursement policies should provide an effective, stable, predictable, transparent, and sustainable pricing environment for pharmaceutical products. They should internalise national priorities for health and industrial policy, including cost containment, employment, innovation, and trade promotion. In this context, it is important for the Cypriot Ministry of Health to transition from the exclusive reliance on policies with noted shortcomings, such as external price referencing, to more efficient and flexible policies both on the supply- and the demand-side. For example, the system of pricing can be refined to deliver prices that are appropriate given Cyprus' income levels. The establishment of a system of reimbursement will enable the competent authorities to negotiate reimbursement prices based on a variety of criteria, including clinical and cost-effectiveness, and establish agreements with manufacturers that are in the country's best interests, both for on- and off-patent products. A number of demand-side policies also need to be introduced, including: electronic prescribing system, generic prescribing, generic substitution, incentives to prescribers (both financial and non-financial), and a cost-sharing policy. However, many of the long-term solutions require stakeholder consensus and, possibly, concessions, technical and analytical capacity development, and changes in the operating environment for pharmaceutical products at the systemic level.

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