

LET'S TALK ACCESS!

WHITE PAPER ON TACKLING CHALLENGES IN
ACCESS TO MEDICINES FOR ALL CANCER
PATIENTS IN EUROPE



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ECL ACCESS TO MEDICINES TASK FORCE

Established in 2016, the ECL Access to Medicines Task Force advocates for equal access to cancer treatments for all cancer patients in Europe. The Task Force's goals, defined in the Declaration of Intent, are to reach access to high value innovative medicines, transparent and fair pricing of medicinal products, improved patient participation and sustainability of healthcare systems. The Task Force strongly believes in the power of dialogue. We urge all policy-makers and stakeholders to work together and push for equal access to high quality treatments improving both survival and the quality of life of cancer patients.

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EXECUTIVE SUMMARY

There have been significant advances in treatment of cancer in the past decades, however, equal access and affordability of innovative therapies remain a challenge. With aging population, rising cancer incidence, fast growing prices of cancer treatments and uncertain sustainability of healthcare budgets, issues with patients' access strike all over Europe, from East to West, from North to South. In this White Paper, the ECL Access to Medicines Task Force elaborates on the most important challenges in access to medicines and suggest solutions for decision-makers in four areas:



1. DISPARITIES IN AVAILABILITY OF CANCER TREATMENTS

Differences between medicines coverage occur primarily due to their high prices, manufacturing and distribution issues, parallel trade or the business strategy of the pharmaceutical industry. Disparities are apparent primarily between lower- and higher-income countries, but can also occur within one country, between its regions.

To tackle these disparities, policy-makers should:

- i. Invest in establishment of oncology centres and centres of excellence specialising in treatments of (rare) cancers and encourage sharing of expertise through the European Reference Networks (ERNs);
- ii. Conduct a high quality health technology assessment (HTA) to determine high value treatment which should be given a priority access to patients;
- iii. Compare availability of treatments and actual prices between European countries;
- iv. Impose trade restrictions on parallel trade in the European Single Market where access to medicines for local population is at stake; and
- v. Regulate the business strategy of pharmaceutical industry and ensure automatic launch of products in all EU Member States after their regulatory market approval.



2. HIGH PRICES OF CANCER TREATMENTS

This chapter puts the growing prices of cancer medicines in question, as well as the unsustainability of the current pricing system. It further looks at the impact of European patent protection and the potential of the use of biosimilars on patient's access to medicines.

To address high prices, the ECL Access to Medicines Task Force advises decision-makers to:

- i. Define a fair price and follow a sustainable pricing model;
- ii. Measure the extent of public investment in R&D and ensure taxpayers do not pay twice or thrice;
- iii. Continue a critical review on the functioning of European IP system; and
- iv. Encourage swift uptake of biosimilars after their marketing authorisation.



3. REGULATORY AND SYSTEMIC ISSUES

Chapter three focuses on the medicine going through the marketing authorisation (MA), health technology assessment (HTA) and pricing and reimbursement (P&R) to reach the patient. The paper questions the quality of data used for MA and HTA, as well as the lack of transparency in the P&R process.

The paper urges decision-makers to:

- i. Ensure high quality benefit-risk assessment of relevant endpoints before granting market access;
- ii. Support sustainable EU HTA collaboration; and
- iii. Achieve a fair level playing field between governments and pharmaceutical companies to strengthen the position of governments and payers in pricing negotiations.



4. FLAWED INNOVATION MODELS

Not everything new is innovative. The last but not least chapter scrutinises the (in)effectivity of innovative models to address high unmet medical need. The chapter further questions the quality of new medicines which are often failing to improve overall survival and quality of life of cancer patients.

To answer the complex question of re-thinking the innovation model, the paper calls decision-makers to:

- i. Invest in public research covering unmet medical need;
- ii. Harmonise policy and practice in the area of emerging targeted therapies; and
- iii. Ensure well-functioning patient enrolment in clinical studies.

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INTRODUCTION

Medicines play a very important role in improving quality and length of life of cancer patients. The field of cancer therapies is evolving rapidly and more and more innovative medicines reach European market every year. These therapies enable many patients to survive cancer or live longer with the disease.

Yet, there is no mere reason for euphoria as there are still many obstacles to overcome. The rapid acceleration in the development of innovative medicines brings at the same time great dilemmas, associated with the limited access caused among others by the unprecedentedly high prices. The discussion about expensive medicines touches the patient at heart. Due to current developments and frequent reports in the media about poor accessibility to these drugs, cancer patients lose confidence in receiving the best treatment available. **Moreover, despite promised value and innovative price tags, clinical efficacy and the effect on patients' quality of life often proved to be marginal in the real life setting.**

The ECL Access to Medicines Task Force advocates for equal access to effective medicines for all cancer patients in Europe. To achieve our mission, the Task Force has agreed on five long-term goals.¹ The purpose of this document is to address the first goal, which states that 'all effective and innovative cancer treatments now and in the future should be accessible to all European patients. Patients cannot suffer from a dysfunctional system with unsustainable financial and pricing arrangements in the prescription of medicines.' After an extensive inventory and categorisation of different obstacles, we are pleased to present the following White Paper elaborating on the four most important challenges in access to medicines, i.e., (i) disparities in availability of cancer treatments; (ii) high prices of medicines; (iii) regulatory and systemic issues; and (iv) flawed innovation models. The Paper further draws possible solutions for named challenges, which will serve as basis for ECL's advocacy action at European and national level.

Chapter 1

Disparities in Availability of Cancer Treatments

Disparities in availability of cancer treatments, particularly between Western and Eastern Europe, can often occur due to high prices of new medicines, product manufacturing and distribution issues, parallel trade or pharma business strategy. In some countries, differences in treatment availability and access to medicines, diagnosis and care can occur regionally, depending on the available expertise and infrastructure or individual hospital management.

1.1 DISPARITIES BETWEEN EUROPEAN COUNTRIES

The European Society for Medical Oncology (ESMO) survey conducted in 49 European countries showed substantial differences in out-of-pocket costs for patients and the formulary and actual availability of many cancer medicines. For example, profound differences were found in melanoma and renal cell cancer cases, where recent biological treatments reimbursed in Western European countries were not available at all or at a full cost to the patient in most of Eastern Europe.² Another study of metastatic melanoma conducted in 30 countries found that **more than 5,000 patients in Eastern Europe (27% of the metastatic melanoma patient population in Europe) did not have access to the first-line innovative treatment due to its high cost.**³

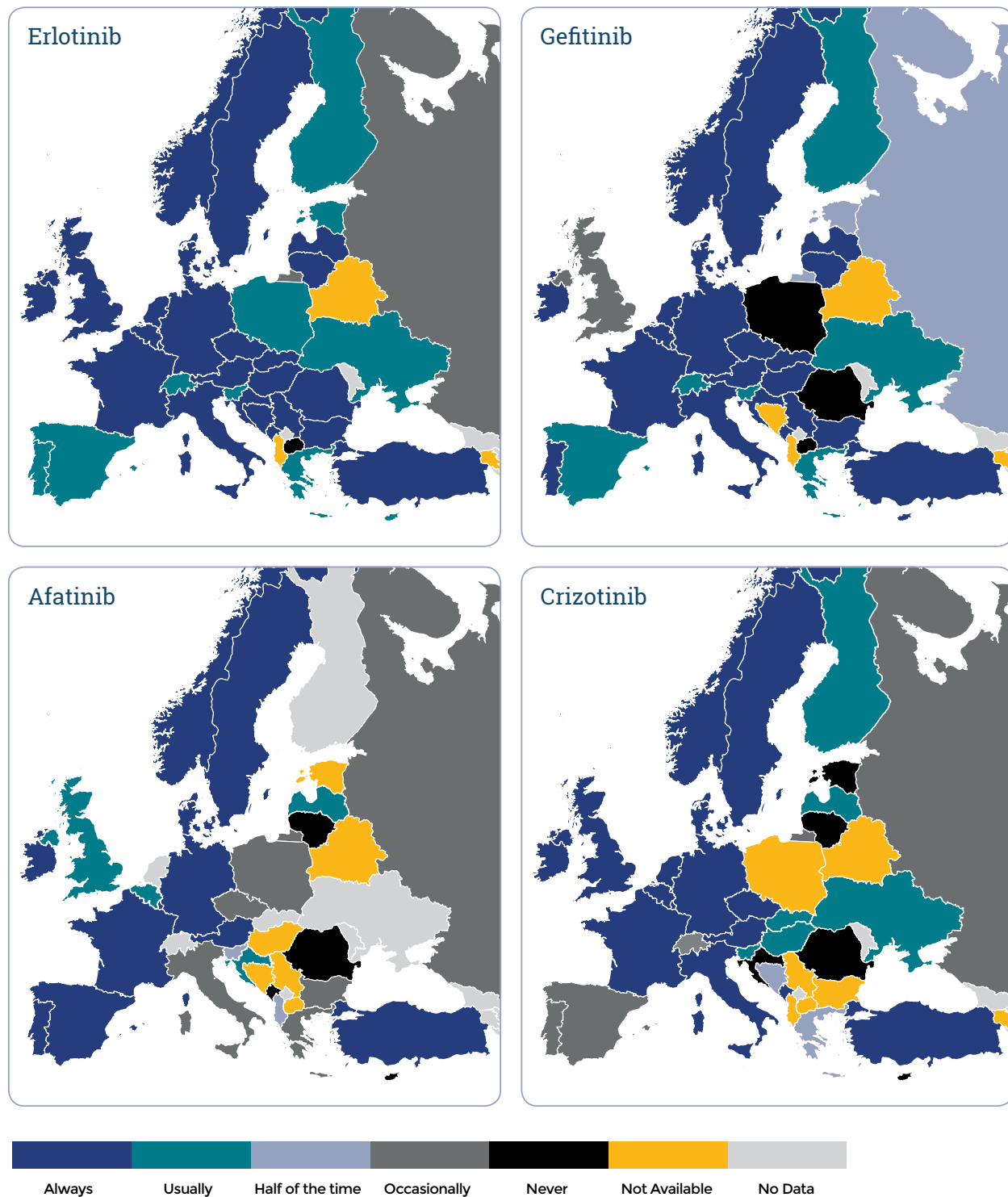
Furthermore, in lung cancer, metastatic breast cancer and colorectal cancer, large disparities in availability and out-of-pocket expenses occurred for different subgroups of patients. For example, in the case of lung cancer, most of the relevant chemotherapy options were available in both Western and Eastern Europe, but there were major discrepancies in the availability of targeted therapies for patients suffering from non-small-cell lung cancer subtypes with EGFR or ALK mutations.⁴

According to the authors, the cost of these treatments was a major factor explaining the disparities between Eastern and Western Europe. The survey further found that even low-cost cancer medicines, such as tamoxifen and cisplatin were not always available due to manufacturing and distribution issues caused by ineffective supply mechanisms.⁵

In addition, parallel trade contributes to drug shortages in countries characterised by lower medicines prices. Among others, Greece, Romania and Poland are known to export large quantities of pharmaceuticals to higher-income EU Member States. Unfortunately, these exports are on the rise and regularly interfere with domestic needs, causing shortages and preventing access to these medicines for local patients. In some cases, however, parallel import may serve as a temporary solution to drug shortages as it allows access to other markets when domestic stocks become insufficient.⁶

Last but not least, business strategy and lack of financial motivation of the pharmaceutical industry to launch their products in lower-income countries challenge equal access to medicines in all of Europe.⁷

Availability of Lung Cancer Treatments in Europe 2016



Based on: Cherny, N., et al. (Annals of Oncology, vol. 27(8), 2016)

1.2 DISPARITIES WITHIN EUROPEAN COUNTRIES

Several countries experience regional variation in patients' access to diagnosis and treatment.⁸ This is not only related to the use of medicines, but also other treatment interventions such as neoadjuvant (chemo) radiation or the centralisation of surgery which improves patient selection, peri-operative care, surgical experience and decreases failure in case of complications.⁹ Moreover, there is a lack of palliative care and continuing care facilities, and the organisation of care remains unequal in terms of access to medical supply - both in terms of practitioners and technical platforms.

The lack of expert centres for complex surgeries such as pancreatic, oesophagus and rare cancers has occurred as a source of further disparities.¹⁰ In many countries, care centres are concentrated in populated areas, leaving rural areas with high unmet medical need (e.g., Italy, Greece, Latvia, Croatia, Romania).¹¹

Variations may be related to the healthcare system itself (e.g., in the Netherlands, budgetary deficit in hospitals can lead to a limited access), but also to individual preferences of oncologists.



What shall decision-makers do to address disparities in availability of cancer treatment?

01

Invest in establishment of oncology centres and centres of excellence specialising in treatment of (rare) cancers and encourage sharing of expertise through the European Reference Networks (ERNs).

Specialised centres of excellence proved to reach higher patient outcomes than general hospitals.¹² Transforming facilities into functioning cancer centres or developing new facilities with research commitment and scientific collaboration will improve cancer services and results. Experts from EU Member States shall be encouraged to share best practices, particularly in cases of rare and complex cancers, and where knowledge gap and lack of expertise occurs.

- i. On the national level, invest in regional capacity building and infrastructure to ease patients' access to diagnosis, treatment and care during the whole patient pathway including quality (para)medical, psychosocial and palliative care and rehabilitation.
- ii. Use EU structural funds to establish centres of excellence, particularly in Central and Eastern Europe.
- iii. Continue investment in ERNs (EURACAN and PaedCAN) and expand their focus to more cancer areas.

02

Conduct a high quality health technology assessment (HTA) to determine high value treatment which should be given a priority access to patients.

High price was determined as the most common reason for therapies not being available in some European countries. There should be a good balance between sustainability of healthcare systems and patients' access to high value innovative treatments. High quality HTA is necessary to measure the added value of innovative therapies which should be recommended for reimbursement at the national level.

- i. Support the establishment of sustainable European cooperation on HTA and mandatory joint clinical assessment with pooled expertise from EU Member States.
- ii. Participate in voluntary cooperation on HTA in other areas such as non-clinical aspects of assessment.
- iii. Participate in related initiatives of the HTA cooperation and joint pricing negotiations initiatives (BENELUXA, Valletta Declaration) such as horizon scanning and knowledge sharing.

03

Compare availability of treatments and actual prices between European countries. (further elaborated on in Chapter 2)

- i. Share knowledge on actual prices between all payers, to ensure higher bargaining power of governments in the pricing negotiations.
- ii. Participate in joint price negotiations initiatives (BENELUXA, Valletta Declaration).
- iii. Prices shall be transparent and differential, proportionate to country's GDP per capita. System of confidential discounts negotiations shall be abandoned.

04

Impose trade restrictions on parallel trade in the European Single Market where access to medicines for local population is at stake.

Parallel imports and exports of medicinal products are a lawful form of trade within the Single Market and result in cheaper medicine supply in some EU Member States (e.g., Denmark). However, parallel trade often causes medicine shortages in lower-income countries and thus creates an obstacle for access to such treatments for local patients. It is therefore necessary to establish a fine balance between parallel trade helping a situation in one country and full patients' access in another MS.

- i. Establish a transnational database with country-specific stocks of medicinal products showing medicines available for export.
- ii. Pose legislative restrictions on parallel trade where patients' access and public health of local population is threatened.

05

Regulate the business strategy of pharmaceutical industry and ensure automatic launch of products in all EU Member States after regulatory market approval.

After a regulatory approval, pharmaceutical industry launches medicines in high-income countries first, to ensure the possibility of asking the highest possible price for their product. Subsequently a reference pricing system is used.

- i. Regulate pharmaceutical business strategy so all medicinal products are automatically launched in all countries in the EU after the EMA approval.

Chapter 2

High Prices of Cancer Treatments

Prices of cancer treatments have been rising for the past two decades. Clear lack of transparency and de-linkage between the price of R&D and products once marketed are hardly to be overlooked. High prices and the burden they lay on European healthcare budgets are the primary obstacle for patients' access to innovative cancer treatments.

New medicines provide hope. Yet expensive drugs often fail to deliver meaningful value to patients and society, marginally improving quality of life and overall survival, while still putting pressure on the sustainability of the entire health economy. Furthermore, the full potential of competition and related price drops have been contested by European IP protection system as well as the lack of information about availability and uptake of biosimilars.

2.1 RISING PRICES OF CANCER MEDICINES

The growth in prices of cancer medicines is expected to exceed the growth in total cancer spending. From 2010 to 2020, total expenditure is estimated to increase by 26%, while spending on cancer drugs will rise by 50%.¹³ For example, in Denmark, expenditures in cancer medicines increased from €26 million in 1998 to €309 million in 2016, and in the same period monthly prices for new cancer medicines increased from €2,960 to €9,400 per patient, i.e. prices grew by 7% per year.¹⁴

Pharmaceutical industry is dependent on the price growth to maximise their profits and margins: 1% of price increase translates to 8% of profit increase.¹⁵ Sydbank, one of the largest Danish banking groups, performed an analysis of the pharmaceutical industry and found that in general 30% of pharma

turnover results in profit.¹⁶ Similarly, in 2016, health technology was categorised as the most profitable of all industries by Forbes, with 21.6% of net profit margin.¹⁷ According to Credit Suisse, a Swiss multinational investment bank, list prices for prescription medicines grew by 9.8% in 2016 and net prices (profit after discounts to the pharmacy benefit managers) increased by 6%. Credit Suisse reported that such price increase played a critical role in pharmaceutical companies' growth.¹⁸

There is a clear lack of transparency in the true cost of R&D as well as the extent of related public spending.

Big Pharma's Revenues and R&D Investment 2014

World's largest pharmaceutical firms					
Company	Total revenue (\$bn)	R&D spend (\$bn)	Sales and marketing spend (\$bn)	Profit (\$bn)	Profit margin (%)
Johnson & Johnson (US)	71.3	8.2	17.5	13.8	19
Novartis (Swiss)	58.8	9.9	14.6	9.2	16
Pfizer (US)	51.6	6.6	11.4	22.0	43
Hoffmann-La Roche (Swiss)	50.3	9.3	9.0	12.0	24
Sanofi (France)	44.4	6.3	9.1	8.5	11
Merck (US)	44.0	7.5	9.5	4.4	10
GSK (UK)	41.4	5.3	9.9	8.5	21
AstraZeneca (UK)	25.7	4.3	7.3	2.6	10
Eli Lilly (US)	23.1	5.5	5.7	4.7	20
AbbVie (US)	18.8	2.9	4.3	4.1	22

Source: GlobalData / Anderson R, 'Pharmaceutical Industry Gets High on Fat Profits', BBC 2014

However, rising prices do not reflect investment in R&D. Great inefficiency occurs in drug development where many companies perform similar trials with comparable medicines without sharing generated data, and thus create enormous redundancy in clinical studies.¹⁹ Industry often points out the costly development of innovative medicines and forgets to consider public investments in R&D (even if significant).²⁰ Similarly, according to a study by Doctors without Borders, the cost of development of new medicines ranged from \$50 to \$186 million (taking failure into account).²¹ On the other hand, the Turf Center, a pharma-sponsored American think tank, assessed that R&D could cost up to \$2.9 billion (including time costs, post-approval research).²² Thus, there is a clear lack of transparency in the true cost of R&D.²³

The American National Bureau of Economic Research (NBER) found that for 58 cancer drugs approved between 1995 and 2013 the launch prices, adjusted for inflation and drugs' survival benefits, increased by 10% (about \$8,500) per year.²⁴ An analysis by University of Liverpool's pharmacologist Andrew Hill found that Americans pay up to 600 times what the medicines cost to manufacture. For example, Gleevec® costs only \$159 a year to produce, but US insurers pay \$106,000 for a year's worth of treatment. Comparably, Tarceva® costs \$236 to produce against a US price of \$79,000, and Tykerb® costs \$4,000 to produce against a price of \$74,000.²⁵

Similarly, enzalutamide (Xtandi®), a very effective medicine for patients with advanced prostate cancer, was introduced in Denmark in September 2013 at a cost of €36,500 for an average treatment period of about 8 months. The R&D cost component was estimated at €265, if total R&D costs were calculated for all patients worldwide during the patent period.²⁶ Together with the delivery costs of €2,450 (production plus 100% overhead expenses for marketing and sales), and with a profit of €3,250 (120%) a fair price could be set at €5,970. However, since Pfizer bought enzalutamide from Medivation for \$14 billion, converting this acquisition cost to the price component added €6,615 (120%) to the price, suggested a fair price of €19,950. Regrettably, we still observe an extra of mark up of €16,550.²⁷

ECL Access to Medicines Task Force believes that a fair price is transparent, understandable, cost-effective, affordable and based on objective factors such as R&D investment, delivery, marketing and sales costs, and a clearly defined profit margin connected to the therapeutic value. Fair prices are profitable enough to ensure innovation as well as sustainable.

Price controversies and disproportionality is also connected to the new CAR T-cell therapies, a high value blood cancer treatment. In 2012 Dr. June, a major contributor to the use of CAR-Ts in cancer care, said to the New York Times that producing engineered T-cells would cost about \$20,000 per patient.²⁸ However, Novartis' Kymriah® was approved by the FDA in August 2017 with a list price of \$475,000 and Gilead/Kites's Yescarta® approved two months after Kymriah® was priced at \$373,000.²⁹ Industry claimed high expenditures were connected to this personalised medicine's R&D, but according to the NGO Knowledge Ecology International (KEI), the US National Institute for Health (NIH) invested more than \$200 million in CAR-T R&D between 1993 and 2017. By March 2017, 91% of CAR-T trials had an academic sponsor.³⁰ CAR T-cell

therapies were market approved in the EU on 27 August 2018. Significant budgetary constraints of European payers can be expected.³¹

New promising medicines developed by smaller companies are often purchased by big pharma (as showed in examples of Xtandi® and Yescarta®) at a very high acquisition cost which are reflected in the cost of new treatments. It can be argued that enzalutamide is one of the more effective cancer treatment with an overall survival gain of 4,8 months per patient. Therefore, under the current functioning of the pharmaceutical market, the high price was justified in 2013 when the drug was introduced. However, we can observe high prices even when medicines do not provide additional value to cancer patients in survival or quality of life gains.³²

2.2 EFFECT OF IPR PROTECTION

According to the European Patent Office (EPO), pharmaceuticals and biotechnology belong to the most patent intensive industries. Companies file patents in order to gain monopoly on the development and sale of specific medicinal products. This prevents access of generics and biosimilars to the market and keeps prices at a high level. In addition to patents, the EU offers additional incentives to steer pharmaceutical innovation. These are namely: (i) the Supplementary Protection Certificate (SPC) which provides additionally up to 5 more years of patent protection; (ii) Regulatory Data Protection (DP) protecting manufacturers' data on quality, safety and efficacy applicable for 8 years starting on the day of marketing authorisation (MA), followed by 2 years of market exclusivity (market protection, MP); (iii) orphan designation for rare diseases offering 10 years of market exclusivity; and (iv) paediatric reward which provides either 6 months extension to SPC or 2 additional years to the orphan market exclusivity. IP incentives can accumulate and innovative pharma tries hard to protect their products from arriving competition.

Some pharmaceutical companies were fined or dragged into lawsuits for trying to avoid generics entering the market or making 'pay for delay' deals with generic companies to keep their products off the market.³³

In the June 2016 EPSCO Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States,³⁴ Health Ministers expressed their concern about the current system and the abuse of IP incentives by pharmaceutical industry. Ministers asked the European Commission to review these incentives to identify the need for potential legislative/policy review. Long awaited study by Copenhagen Economics, a Danish consultancy selected to conduct the review, however failed to draw the link between IP protection and access to medicines. The study, published in May 2018, analysed 558 medicinal products and identified that: (i) length of data protection has declined from an average of 15 years to 13 years during the period 1996 to 2016; (ii) availability of generics and biosimilar may be delayed by SPC, DP and MP and called this trade-off between innovation incentives and generic market access a political decision; and (iii) longer IP protection period have no effect on pricing, and the company will always charge the highest price possible. The report concluded that it would be ideal to secure a sufficient period of protection and reduce uncertainties associated with developing medicinal products in order to incentivise innovation, while finding other ways of curbing high prices.³⁵

A similar study concentrating on the Dutch pharmaceutical market was published shortly after during the same month by Technopolis, an Amsterdam-based consultancy. The study found that IP protection needed to strike a good balance between benefits and costs. For society, these costs consist primarily of higher prices a pharmaceutical company can charge whilst it does not face competition from generic manufacturers, and higher profits it can make. It stated that if a drug

is reimbursed under the public healthcare system, the costs can crowd out other medication or treatment methods, given limited public means. It can also affect the accessibility of medicines to lower income groups. In addition, there are the costs of litigation and rent-seeking in relation to the patent system and supplementary protection mechanisms.³⁶

2.3 SLOW UPTAKE OF GENERIC AND BIOSIMILAR CANCER MEDICINES

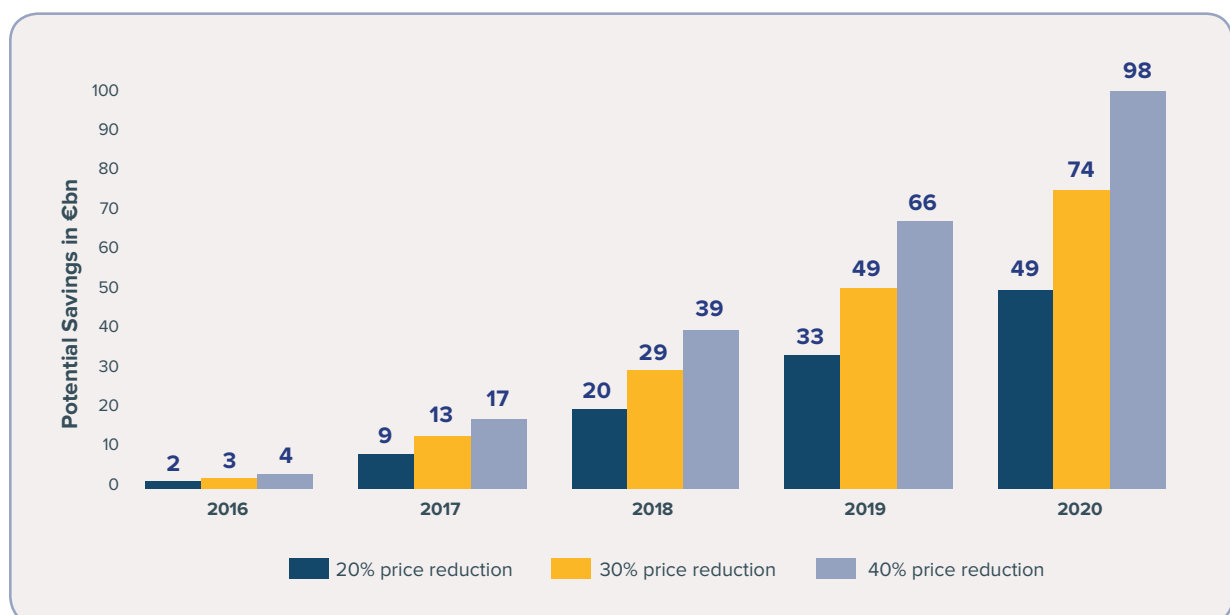
According to IMS Health, a US-based health data service, uptake of biosimilars could lead to cost savings up to €100 billion by 2020 in the US and the 5 biggest markets in the EU.³⁷ However, the uptake of biosimilars after the patent expiry has been rather slow.³⁸ After granting a marketing authorisation at the EU level it is up to the Member States to formulate biosimilar policies.

There are differences in pricing and reimbursement procedures and levels of education of physicians leading to variations in uptake of biosimilars. A survey carried out in 24 countries (of which 20 were EU MS) showed that the full potential of biosimilars was not yet captured and that various hurdles exist in the development of the biosimilar market.³⁹ The main hurdle identified was a lack of knowledge and education among key

stakeholders, especially physicians and patients. It is important that informed decisions can be made. There is a clear need for precise and reliable information from independent institutions and better communication and education on the use of biosimilars. Furthermore, competitive and sustainable pricing is needed in order to incentivise physicians to prescribe biosimilars. Authorities and pharma should collaborate on a national and international level and share information. Last but not least, there should be more support for substitution and switching programs, supported by the industry/insurers. This should also be addressed at the EU level.⁴⁰

In addition to a relatively low uptake of generic drugs in European countries, we observe huge discrepancies in their pricing. A recent study of the London School of Economics

Biosimilar Savings Potential in the EU5 and U.S., for 8 Key Products in 2015-2020



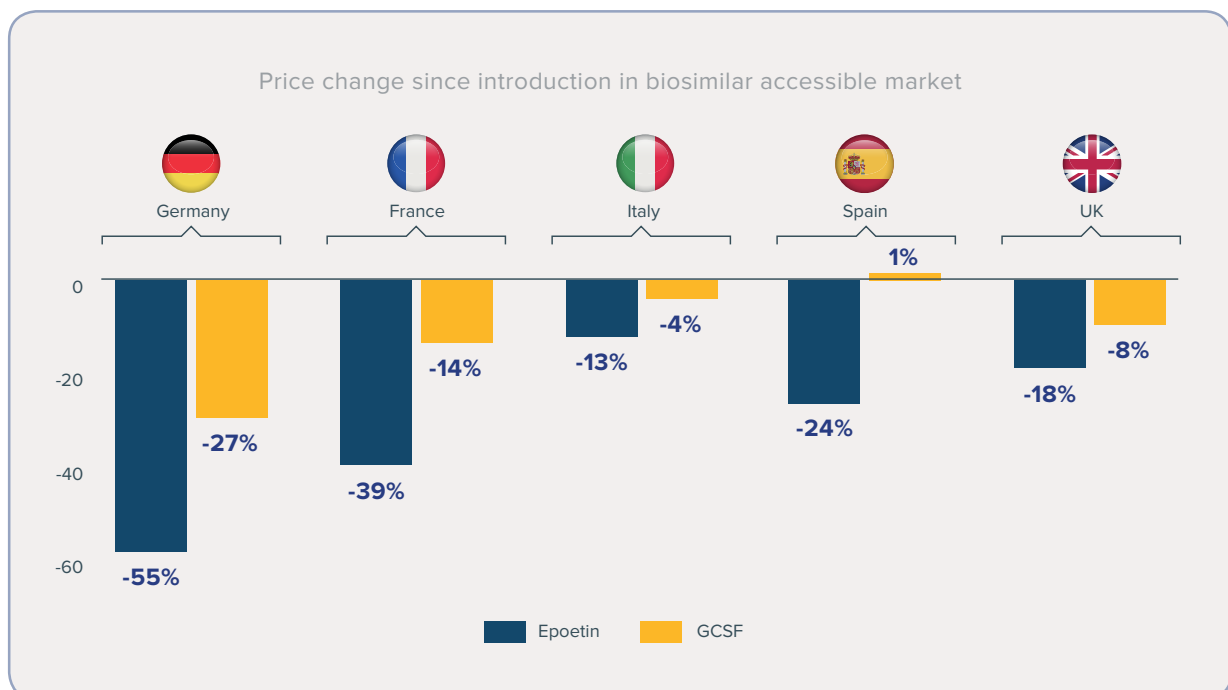
Source: IMS Health, MIDAS, IMS Health Market Prognosis; IMS Institute for Healthcare Informatics, Dec 2015

(LSE) highlighted this pattern by comparing the ex-manufacturer prices of generic products in Europe and the United States. Using a price index, LSE found that prices in Switzerland were on average 2.5 times more expensive than in Germany and more than 6 times higher than those in the United Kingdom. Even more striking was the example of omeprazole (a proton-pump inhibitor) where the price charged by the manufacturer was 30 times higher in Switzerland than in the UK.⁴¹ We can assume that these unexplained differences are not attributable to different living standards, but rather a result of inefficiencies in the generic market. Moreover, prices of generics highly depend on the number of manufacturers. Indeed, for medicines with only one generic manufacturer, the price of the generic does not

differ from the price of the brand-name drug.⁴² In some cases with only one producer, price of the generic even dramatically increased. For example, the price of captopril (medicine for hypertension and heart failure) went up by 2,800% between 2012 and 2013.⁴³ **On the other hand, with two competing manufacturers, the price drop is estimated between 10% and 50%.⁴⁴ With more than 3 manufacturers, the prices further continue to decrease.**

This pattern shows the importance of stimulating the competition on the generic market to achieve lower prices.

Price and Changes Following Biosimilar Introduction



Source: IMS Health, The Impact of Biosimilar Competition, Nov 2015 Note: Analysis based on publicly available prices



How can decision-makers tackle issues with high prices of cancer treatments?

01

Define a fair price and follow a sustainable pricing model.

There is little transparency behind pricing strategies of the pharmaceutical industry and the definition of a 'fair price' remains unclear. At ECL, we believe that a fair price has to be transparent, understandable, cost-effective, affordable and based on objective factors such as R&D investment, delivery, marketing and sales costs, and a clearly defined profit margin connected to therapeutic value. Fair prices are profitable enough to ensure innovation as well as sustainable.

- i. Define what constitutes a fair price and what stakeholders should understand under its different aspects (such as transparency, therapeutic value etc.). Use the WHO definition set at the Amsterdam Fair Pricing Forum in May 2017 as a starting point of the discussion.
- ii. Follow an understandable and transparent pricing model to ensure sustainability of healthcare systems.

02

Measure the extent of public investment in R&D and ensure taxpayers do not pay twice or thrice.

Industry often argues that high prices of medicines are connected to research and development spending. However, the exact extent of often significant public investment in pharmaceutical R&D (public grants, academic research, tax breaks etc.) remains unknown. It is often argued that the society pays twice, first in research and second time to reimburse the product. Payers need to have clear number showing this trend in order to negotiate fairer prices with the industry.

- i. Map and measure public investment in pharmaceutical R&D both on national and EU level and use the data during pricing negotiations.

03**Continue a critical review on the functioning of European IP system.**

Even though conducted study on IP incentives did not explicitly link IP protection and access to medicines, it did state that striking a good balance between incentives stimulating R&D activities and societal cost connected to higher prices of medicines under patent protection is a key political decision. Further studies analysing different incentives and related legislative changes will be needed to improve the inefficiencies in the IP system, especially in cases of unnecessary market access delays of generic medicines.

- i. Protect competition by monitoring and imposing fines on companies signing 'pay-for-delay' deals between originator and generic manufacturers.

04**Encourage swift uptake of biosimilars after their marketing authorisation.**

In order to further develop biosimilar market for cancer medicines, more clear and reliable information from independent institutions for both patients and physicians should be developed and distributed.

- i. Develop Q&A documents and platforms to share knowledge and experiences with the use of biosimilars.
- ii. Introduce binding quota or gain sharing policies related to prescription of biosimilars.
- iii. EMA should develop lists and guidelines for appropriate switching options. This guidance on switching between biosimilars should be added in EPAR summary of product characteristics and the SmPC label to provide physicians with needed information.
- iv. Switching programmes should be supported by insurance companies and industry; biosimilar use shall appear in clinical prescribing guidelines.
- v. In addition, national and European medical societies shall offer guidance and trainings; similarly, awareness raising shall be carried out by patient organisations.



Chapter 3

Regulatory & Systemic Issues

Innovative treatments challenge the regulatory system. Indeed, data available at the time of a regulatory approval are often insufficient to show a clear significant benefit and re-assessment (once new data is available) is often neglected. Proper health technology assessment is often missing and lack of transparency prevents governments from conducting effective price negotiations with pharmaceutical industry.

3.1 MARKET APPROVAL

It is necessary to balance the evaluation of safety and efficacy of new medicines, simultaneously with fast market access of treatments in the areas of high medical need. On average, it takes EMA 441 days to issue a marketing authorisation (ranging from 266 to 770 days). After a medicine receives a market approval, the price negotiations with national authorities can take up to two years.⁴⁵

To ensure access to new promising therapies to patients in a timely manner, the EMA initiated programmes such as (i) the PRIME scheme which offers accelerated approval and increased cooperation with a sponsor and the EMA for medicines offering major therapeutic advantage over existing treatments or benefit patients without treatment options; (ii) possibility of applying for a conditional MA in case of medicines where the benefit of immediate availability outweighs the risk of less comprehensive data, for example in the case of serious, debilitating or life threatening disease; and (iii) the use of adaptive pathways aimed at medicines addressing unmet medical needs in specific groups of patients. Oncology accounts for the largest number of acceptance to all the above mentioned programmes. The EMA claimed that all three schemes result in an early access to medicines for patients,

however, from 2006 to 2016, 30 medicines were granted conditional approval of which two were withdrawn for commercial reasons, and the remaining had full market approval pending.⁴⁶ Critical voices question the quality of the supplementary data provided by the drug manufacturers on which the full marketing approval is based. They also question the ethical and clinical appropriateness of allowing patients' access to medicines while being unaware of the full risk-benefit profile.⁴⁷

It is also questionable whether early access schemes are used as intended, or whether they result in patients being exposed to new medicines where the benefits are uncertain and safety issues unknown.

Hoekman et al. suggest that conditional marketing authorisation is not used by the industry as a planned pathway to obtain early access, but merely as a 'rescue option' when research data are not strong enough to obtain full MA.⁴⁸

3.2 HEALTH TECHNOLOGY ASSESSMENT

Before reimbursement of a new medicine takes place, authorities often require health technology assessment (HTA) of all or at least the most expensive new medicines (applicable to a large extent to cancer drugs). HTA provides a way of assessing added value of medicines (or medical devices and other health technologies) and offers recommendations for payers whether or not to reimburse the product. HTA provides decision-makers with objective information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective. HTA is performed at the national level, however, not all countries have the capacity to perform thorough time-consuming HTA for every new medicine/indication. Moreover, conducting HTA of the same medicine in several countries results in duplication and an inefficient use of scarce resources.

Similarly to marketing authorisation, HTA is often based on trial data from pivotal studies led by pharmaceutical industry, which naturally try to demonstrate the efficiency of the new drug.⁴⁹ Consequently, health technology assessment is based on data gained from a selected group of patients with more men, younger population, and very few comorbidities.⁵⁰

Since 2004 efforts were made to deepen cooperation on HTA in Europe. EUnetHTA, a network of HTA bodies in the EU + Norway and Switzerland, was established to develop reliable, timely, transparent and transferable information to contribute to efficient HTA process.⁵¹ In January 2018, the Commission introduced a proposal for EU-wide HTA cooperation with joint clinical assessment to improve current HTA process in most EU Member States and avoid unnecessary duplication.⁵² Currently, the proposal is being negotiated at the EU institutions and many questions connected to the joint clinical assessment remain to be answered.

At ECL we believe that an adoption of a regulation establishing sustainable HTA cooperation will improve the quality of assessment by pooling expertise and ultimately increase access to high-quality medicines for all patients in Europe.⁵³

3.3 ISSUES IN PRICING AND REIMBURSEMENT SYSTEM

Information asymmetry and a lack of transparency lead to inefficient price negotiations, thereby compromising an effective healthcare spending.

Negotiations as well as achieved discounts are kept confidential between the pharmaceutical company and the different payers, leading to great variations in the price-setting of cancer medicines in European countries.⁵⁴ There exists an informational asymmetry, where the industry knows the drug prices in all countries, but national payers do not have access to such data beyond their borders.⁵⁵

Thus, pharma has a dominant position in the price negotiations and countries are left in a prisoner's dilemma position. It is difficult for a single government to take appropriate measures to ensure lower prices.⁵⁶

Further problems occur due to international (external) reference pricing rules which give power to set prices to governments through the reference countries. Multinational pharmaceutical companies can thus indirectly influence the price through their cross-country pricing strategies (including managed entry agreements that keep the effective prices in each market confidential).⁵⁷

It is important to note that governments have to protect employment in the pharma sector and at the same time reconcile saving money in health insurance. For instance, the large number of pharmaceutical companies in Denmark generating 90,000 jobs, 30% of privately funded research and export greater than export of any other product (14% total), is making pharma a strong negotiator.⁵⁸

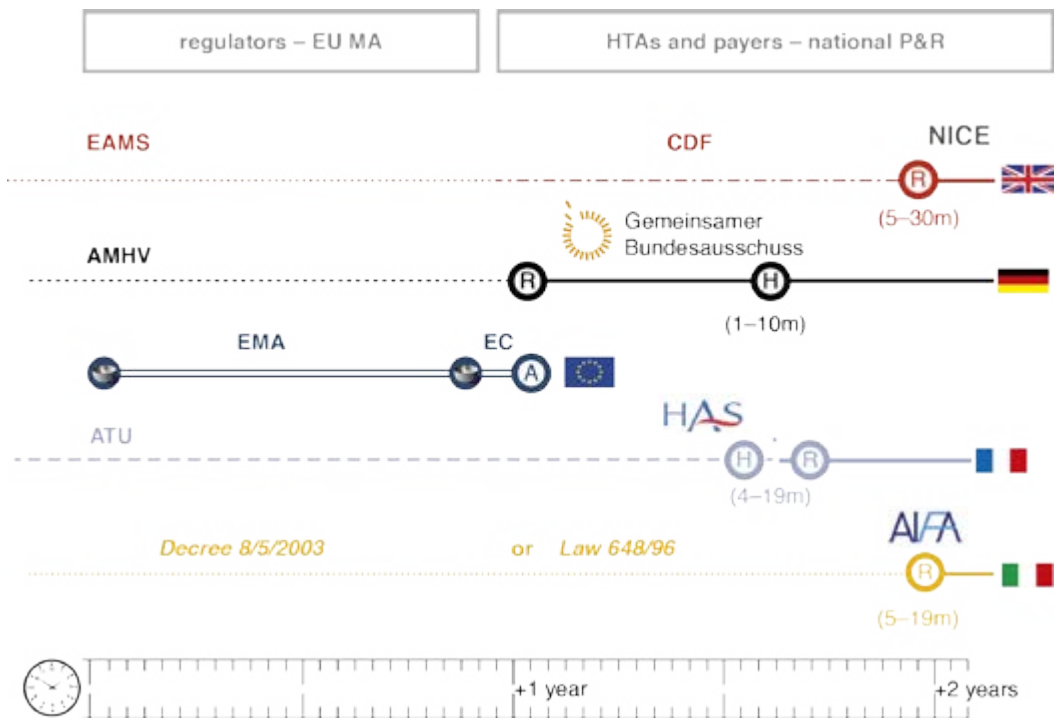
Furthermore, countries with private health insurance companies experience a dual government vision: market forces vs. tackling expensive medicines. In the Netherlands, the idea of installing a private health insurance was to enable a more market-oriented approach for health insurance companies in the lead of the price negotiations. However, following the fraction of expensive drugs, the government took the lead by negotiating directly with the industry to demand discounts. Insurance companies accepted this policy, but negotiate simultaneously with the industry to obtain even larger discounts. Consequently, negotiations happen at various levels: Ministry of Health, Welfare and Sport (VWS), insurance companies (each on their own, together or each of them together with a number of hospitals) and at the hospital level (at individual hospital levels or purchase combinations). The outcome of all negotiations is confidential and only the industry has access to the actual price.⁵⁹

In 2016 the Dutch authorities only reviewed nivolumab, palbociclib, ibrutinib and pembrolizumab, while in total 37 new products/indications were registered in oncology, hence only a minority of drugs was reviewed, with the rest automatically forwarded into the reimbursement system.⁶⁰ However, due to the rising costs of medicines, the Dutch Minister for Medical Care Bruno Bruins announced that as of 1 July 2018 all new medicines that cost more than €50,000 per treatment per year or in total more than €40 million will be excluded from the system of automatic reimbursement. This gives the ministry a chance to first negotiate about the high price with the company before the drug gets reimbursed.⁶¹ In the meantime, the compassionate use programme allows patients' access to medicines undergoing the price negotiation. Nevertheless, the Dutch government has decided to keep the gate

to the covered healthcare package closed for some new medicines under the price negotiation, to enhance the pressure on the industry to close the negotiations and to gain the health insurance coverage.⁶²

Furthermore, reimbursement system poses issues ranging from the lack of meaningful reimbursement criteria, the lack of time/expertise of payers/assessors and delays in research and approval of variations and new indications. Payers regularly have to deliver the work within rigid timeframes which are often extended, e.g., due to understaffing or difficult price negotiations. In addition, once a drug is reimbursed, it often stays reimbursed, even when it becomes obsolete (e.g., reimbursement of bevacizumab for women with metastatic breast cancer in Belgium).⁶³

Market Access timeline in the UK, Germany, France and Italy



Graph explanation: Timelines of approval and HTA/P&R decisions for oncological products in EU4. Circles represent the median duration of regulatory authorisation (A) and time points of health technology assessment (H) or reimbursement (R) recommendations/decisions in England and Wales, Germany, France, and Italy, based on median times from EU marketing authorisation (MA) in months (+range) for a basket of cancer drugs (N = 15) with regular approval in the EU in 2011–2013. Solid lines indicate broadly reimbursed patient access within national healthcare systems, following authorisation (DE), formal P&R decisions (IT and FR), or HTA recommendations (EN&W). Dashed lines indicate national early access programmes which can provide bridging mechanisms for reimbursement before MA and/or in the transitional period between MA and P&R.

Source: Martinalbo J. et. al., 'Early market access of cancer drugs in the EU.' *Annals of Oncology*, vol. 27(1), (2016), p.96–105



How can decision-makers improve the system to achieve equal access to high quality cancer treatments?

01

Ensure high quality benefit-risk assessment of relevant endpoints before granting market access.

Regulatory approval as well as accelerated approval schemes are often based on surrogate endpoints and incomplete data from clinical trials. There is a need to follow up with reassessment once new data becomes available.

- i. Allow use of adaptive pathways and accelerated assessment schemes by the EMA as intended, for high unmet medical need only. Prevent misuse of accelerated approval schemes.
- ii. Make sure comprehensive data from well-designed studies with relevant endpoints are delivered in a timely manner to gain full MA.
- iii. Ensure timely re-assessment where conditional MA was awarded.
- iv. While providing scientific advice, where appropriate, request design of comparative trials to ease the work of regulators in assessing added value compared to existing treatments.

02

Support sustainable EU HTA collaboration.

In the context of rising costs of innovative treatments, issues connected to sustainability of healthcare systems and proliferation of me-too medicines bringing negligible therapeutic advances, implementation of a strong European cooperation on HTA will contribute to access to high quality treatment for European patients. Implementation of EU HTA regulation and conducting joint clinical assessment will (i) enable faster and improved access to high value treatments for patients in Europe; (ii) strengthen quality of clinical assessment by pooling expertise from all EU Member States; (iii) reduce duplication and ensure efficient use of resources; (iv) help payers make wise decisions on pricing and reimbursement by providing high-quality assessment; (v) increase transparency in all aspects of the joint HTA process; (vi) steer innovation in areas of unmet medical need and improve business predictability.

- i. Ensure HTA is based on high quality endpoints reflecting relevant patient clinical outcomes and quality of life measures.
- ii. Re-assess the medicine once new data is available to get a clear understanding of added value in the real-life setting.
- iii. Involve patients, healthcare professionals, consumer and public health organisations, and academia in the HTA process to get a clearer understanding on societal needs and preferences.
- iv. Ensure transparency and independence of the HTA system.



Achieve a fair level playing field between governments and pharmaceutical companies to strengthen the position of governments and payers in pricing negotiations.

In order for price negotiations to become equal and fair, there is a need for more sustainable negotiation model. European health ministers shall work together and share information on pricing with their peers on a multi- or bilateral inter-governmental level. This should include prices of new (and innovative) products that might still be under patent protection (or other restriction) and highly innovative medicines. EURIPID can be used as a sharing tool and format.

- i. Abandon confidentiality in pricing negotiations, which does not allow governments to share information on ministerial level.
- ii. Allow and actively use EURIPID for information sharing.
- iii. Participate in initiatives encouraging joint price negotiations (BENE-LUXA, Valletta Declaration) to increase governments' bargaining power.
- iv. Set a clear and transparent reimbursement criteria based on high quality clinical and non-clinical assessment (full HTA). Involve patient and other stakeholders in the criteria setting.
- v. Re-evaluate the added value of previously reimbursed treatments in order to prevent investment in technologies which became obsolete.

Chapter 4

Flawed Innovation Models

Not all new medicines are innovative. European market is being flooded with me-too drugs based on prospected high return on investment while unmet medical need remains unaddressed. It is necessary to invest in public research and explore options of public-private partnerships. Moreover, in the age of personalised medicines and combination therapies, the current structure of clinical trials as well as data collection and analysis needs to be adjusted.

4.1 HIGH UNMET MEDICAL NEED

R&D of cancer medicines depends largely on randomised clinical trials (RCTs) led primarily by the industry. Industry-sponsored comparative assessments systematically yield favourable results for investors' interests, especially in the case of noninferiority designs.⁶⁴ Industry often focuses on development of 'me too' medicines and with governments not being directly and strategically engaged in drug development, a mismatch between health priorities and private pharmaceutical research occurs.

In fact, wrong incentives drive innovation. Pharmaceutical companies are owned by shareholders who expect return on their investments. The development of new promising therapies may be linked to high earnings, but also represents high risks such as loss of confidence by the stock investors resulting in a drop of the stock value of the pharmaceutical company.

Thus, focusing on 'me-too' medicines represent a secure way to lower the risks associated with the development of new treatments and ensures return on investment.⁶⁵ Consequently, this mechanism brings many medicines with marginal added value instead of a real breakthrough innovation.

An analysis of 71 consecutive cancer medicines approved for treatment of patients with solid tumours between 2002 and 2014 found that the median improvement in the duration

of overall survival (OS) and progression-free survival (PFS) was 2.1 months and 2.5 months, respectively.⁶⁶

Similarly, a British Medical Journal study from October 2017, which analysed the efficacy of 48 new treatments approved for 68 indications by the EMA between 2009-2013, showed that only 35% (24 indications) resulted in prolonged survival ranging from 1 to 5.8 months (2.7 median). Moreover, out of the treatments associated with the prolonged survival, only 48% (11 indications) were deemed to be clinically meaningful according to ESMO standards. Only 10% (7 indications) showed improvement in the quality of life at the time of market approval. In conclusion, only 51% of indications (35) were associated with improved survival or quality of life, whereas most approvals were based on improvements in surrogate endpoints (mostly progression free survival), with lack of improvements in endpoints such as survival and quality of life.⁶⁷ Moreover, benefits of these agents in a 'real-world' patient population are even smaller than those observed in patients enrolled in clinical trials. This is due to the generally older age and greater number of comorbidities among most real-world cancer patients than in the carefully selected participants in clinical trials.⁶⁸ Well-designed studies with sufficient follow-up time and relevant end-points with proper assessment of safety issues are necessary to allow assessment of the benefit-risk profile of new cancer medicines both at the population level and for individual patient groups.

4.2 PERSONALISED MEDICINES, COMBINATION THERAPIES & ALTERNATIVE STUDY DESIGNS

There is a need for newer, more flexible study designs, and for parallel evaluation of both the cancer medicine and the accompanying diagnostic assessment tool. Data demonstrate that personalised medicines improve clinical outcomes. However, the implementation of personalised medicines regime requires changes in oncology practice, regulatory standards, approval and modification in reimbursement policies as well as different way of data collection, integration and analysis. One of the limiting factors for personalised medicines is the slow progress in translational research caused by regulatory constraints and the lack of funding.

In addition, the movement toward personalised medicines and the changes in the clinical trial strategy requires collaboration and consensus between academia, pharma and regulatory authorities to shift the paradigm toward building registries with data measuring patient outcomes rather than administrative processes.⁶⁹

A major concern with personalised medicine is how to determine whether the prescribed targeted therapy, based on tumour abnormalities and independent of location and histology, would improve patient outcomes.

This requires prospective validation before implementation in clinical practice, and clinical researchers facing the challenge of interpreting vast amounts of data. The challenge is to design the most appropriate clinical studies to validate the hypotheses - not only the drug needs to be investigated but also the biomarkers are vital in this respect. Clinical research should balance cost, strength of basic science and preclinical data and feasibility in the development of clinical trials.⁷⁰

Last but not least, alternative studies such as drug-repurposing, consisting of finding new indications for existing medicines, can serve as effective tools toward more sustainable innovation system. This treatment option is currently not maximised due to the lack of financial incentives for pharmaceutical industry. However, the potential for patients is huge, as no changes are required for currently available medicines. Several generic medicines have proven to help the treatment of cancer, for example aspirin prevents the immune destruction, heparin opposes the invasion process of metastatic cells, and minocycline combats genome instability and mutation.⁷¹



Where shall decision-makers start to steer real innovation?

01

Invest in public research covering unmet medical need.

More funding for public research should be awarded in areas of high unmet medical need where there are not enough financial incentives to steer private investment.

- i. Invest in alternative R&D models including drug-repurposing and public-private partnerships.
- ii. Offer more incentives (patent buy-outs, prizes etc.) in public research to encourage breakthrough innovation.

02

Harmonise policy and practice in the area of emerging targeted therapies. Ensure well-functioning patient enrolment in clinical studies.

In order to address the regulatory need for support of personalised medicines, newer and more flexible clinical study designs based on consensus between academia, pharmaceutical industry and regulatory authorities are necessary. In addition, outcomes-base standardised data collection, integration and analysis are needed.

- i. Patient shall be involved in every step of the clinical trials process: setting of priorities and selecting proposals, study design, organisation of trials (e.g., to improve participant access), preparation and evaluation of the information provided to participants, post-study evaluation, (eg., of the participant experience) and dissemination of the results.
- ii. Patients have to be informed about clinical trials that may be relevant for them, in their own country and abroad. Cross-border regulatory, practical and financial obstacles for patients shall be removed.

ABBREVIATIONS

- AIFA** - Agenzia Italiana del Farmaco (Italian medicines agency)
- ALK** - Anaplastic Lymphoma Kinase
- AMHV** - Arzneimittel-Härtefall-Verordnung (German hardship case programme)
- ATU** - Authorisation Temporaire d'Utilisation (French temporary authorisation for use)
- CAR-T** - Chimeric Antigen Receptor T-Cell
- CDF** - Cancer Drugs Fund UK (until 2016)
- DP** - Data Protection
- EAMS** - Early Access to Medicines Scheme UK
- EC** - European Commission
- ECL** - Association of European Cancer Leagues
- EGFR** - Estimated Glomerular Filtration Rate
- EMA** - European Medicines Agency
- EPAR** - European Public Assessment Reports
- ERN** - European Reference Network
- ERN EURACAN** - European Reference Network for Rare Adult Solid Cancer
- ERN PaedCAN** - European Reference Network for Paediatric Cancer
- ESMO** - European Society for Medical Oncology
- EURIPID** - European Integrated Price Information Database
- HAS** - Haute Autorité de Santé (French HTA body)
- HTA** - Health Technology Assessment
- IPR** - Intellectual Property Rights
- KEI** - Knowledge Ecology International
- MA** - Marketing Authorisation
- MP** - Market Protection
- MS** - Member State of the European Union
- NBER** - The American National Bureau of Economic Research
- NICE** - National Institute for Health and Care Excellence (HTA body England and Wales)
- NIH** - US National Institute for Health
- P&R** - Pricing and Reimbursement
- R&D** - Research and Development
- RCTs** - Randomised Clinical Trials
- SPC** - Supplementary Protection Certificate
- VWS** - Dutch Ministry of Health, Welfare and Sport
- WHO** - World Health Organization

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