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Project run in close collaboration with Zorginstituut Nederland

FUTURE SCENARIOS ABOUT DRUG DEVELOPMENT AND DRUG PRICING

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HEALTH SERVICES RESEARCH
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- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**
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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
CEO	Chief Executive Officer
CERN	European Organization for Nuclear Research
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
HTA	Health Technology Assessment
KCE	Belgian Health Care Knowledge Centre
MoCA	Mechanism of Coordinated Access to orphan medicinal products
NICE	The National Institute for Health and Care Excellence
PPP	Public-Private Partnership
QALY	Quality-adjusted Life Years
RIZIV / INAMI	Rijksinstituut voor Ziekte- en Invaliditeitsverzekering / Institut National d'Assurance Maladie-Invalidité
WHO	World Health Organisation
ZIN	Zorginstituut Nederland

SCIENTIFIC REPORT

1 INTRODUCTION

Over the last decades the list prices of new medicines have increased significantly. Innovative drugs are often introduced on the market at a very high price. There are indications drugs companies pursue prices towards the upper limit of the “willingness to pay”. Many purchasers (governments, health insurers, etc…) are not really armed to set limits to these prices, nor to set reasonable boundaries to the willingness to pay.

A growing number of observers warn that the current trend of increasing drug prices is not sustainable in the long run. Local healthcare payers increasingly struggle to find the budgets needed to provide coverage for these expensive molecules. The patient and public health may not be well served as a consequence. Public payers are recurrently manoeuvered into difficult moral dilemmas. Clearly, the problem with very high-cost medicines needs to be addressed in a more systematic way and a comprehensive solution is needed to preserve access to valuable drugs to all who need them.

This scenario project - initiated by the Belgian Healthcare Knowledge Centre (KCE) and Zorginstituut Nederland (Dutch Health Care Institute, ZIN) - is an attempt to create a space to freely explore a complex societal challenge. The project seeks to highlight creative scenarios to deal with this predicament. The objective is to explore new drug development and pricing models resulting in more sustainable pricing mechanisms and policies, in consultation with international stakeholders including patients, industry, academics, not-for-profit research organisations, regulators, payers, government representatives from Europe and the US.

2 METHODS

2.1 The use of scenarios in the Drug Pricing project

The project relies on a methodology of future scenario development (also known as 'scenario planning'). Through a practice spanning decades, the scenario method has proved to be a potent instrument to help multi-stakeholder groups come to grips with complex socio-technical ('wicked') problems[1].

The scenario planning methodology emerges from the discipline of strategic foresight. It is complemented by other techniques (such as forecasting, roadmapping, horizon scanning, future search) that can be narrowly considered as futures methodologies[2].

Future scenarios constitute a marked departure from an intellectual position that considers the future essentially to be understandable by mere extrapolation of certain trends in the past. Van Notten (2003) defines scenarios as "consistent and coherent descriptions of alternative hypothetical futures that reflect different perspectives on past, present and future developments, which can serve as a basis for action." Key in this approach is the development of multiple, internally consistent descriptions of future states of affairs and the developments that may lead to them. Contrary to a predictive approach that puts the focus on the single most probable future, the scenario planning approach makes explicit the uncertainty facing decision makers by exploring a range of plausible futures.

Whilst there is a consensus about the basic idea underlying the scenario approach, the resulting practice is characterised by a striking diversity. A cursory survey of documented scenario projects reveals a wide array of approaches, formats and types of deliverables (see for instance the European Foresight Platform with its database of case studies: http://www.foresight-platform.eu). In previous publications we have made a distinction between different types of scenarios[3]:

- Exploratory (or contextual) scenarios that describe alternative developments of the environment (context) in which the planning organisation is embedded;
- Policy or decision scenarios that describe long-term impacts of strategic decisions by the planner;
- Normative scenarios that project desirable or undesirable futures.

We would like to complement this categorisation with a type of scenarios that has received much less attention in the scenario literature: 'typology scenarios'. This is particularly pertinent in the context of the present project with focus on drug pricing. Typology scenarios focus on illuminating distinct, future manifestations of a complex and ill-understood phenomenon (such as: forms of spatial development, novel forms of organisation, novel forms of creating economic value, i.e. business models).

In the drug pricing project we see the deliverable as a set of typology scenarios. Each scenario is in effect a description of a particular business model that meets certain criteria of profitability (for the industry) and fairness (with regard to the drug's target group) and manifests a specific mix of strengths and weaknesses (evaluated against criteria that need to be identified). The rationale behind the business model will very likely be co-determined by exogenous, contextual drivers. The relationship between external drivers and the logic of the business model will also be manifest from the scenario.

We want to conclude this discussion of the appropriate use of future scenarios in the Drug Pricing project by a reference to different goals that can be associated with scenario planning, specifically in a decision-making (policy) context[4]:

- A policy goal: scenarios are developed to offer new perspectives for action and developing novel policy options;
- A political goal: scenarios are developed to legitimise espoused or decided positions and policy;
- A process goal: scenarios are developed to help to create buy-in from stakeholders;
- A knowledge goal: scenarios are developed help to deepen insight and knowledge about a certain issue;
- An organisational goal: scenarios are developed to contribute to the agility and future-orientedness of an organisation.

This project primarily wants to stimulate public debate and offer new perspectives for policy makers. Hence it pursues a policy goal. Additionally, it wants to shed light, in an exploratory way (as a 'thought experiment') on a complex and ill-understood question (knowledge goal). Finally, also the

process dimension is important as stakeholder interests naturally diverg1e and as a result relationships might be characterised by a certain degree of distrust (process goal).

2.2 Recruitment of participants

Given the complex and highly politicized nature of the focus of the project it was felt that a balanced group of experts and stakeholders had to be assembled as contributors and participants to the process of scenario development. The role of participants would be double: they would inject their expertise in the process by way of a one-on-one interview and they would actively join in the process of scenario development during two workshops. It was to be expected that not all experts willing to engage in an interview would be able to make themselves available for the workshops. However, it was felt that around 70% of the interviewees had to be present in the workshops also to ensure a credible and efficient process.

The size of the creative group was dictated by the project's technical focus and relatively narrow time window. Therefore we settled on an approximate number of 30 active participants.

Given the geographic location of the organizers, the focus of the project would be the European drug development and pricing environment. Hence the creative group would mainly have to consist of European representatives. However, as the pharmaceutical industry is a global industry with important decision-making centres in the United States, it was felt necessary to also invite North American participants to the scenario development process.

In terms of sectorial representation the following parties, areas of expertise and groups of stakeholders were identified as relevant contributors to the debate:

- Organizers (KCE/ZIN);
- Belgian and Dutch payers;
- Regulators, Public authorities;
- Experts in the area of Intellectual Property Rights;
- Experts in the area of Drug Development;
- Experts in the area of Corporate Innovation;
- Experts in the area of Health Economics;
- Experts in the area of Business Ethics;
- Pharmaceutical industry;
- Experts on Consumer Protection, Access to Medicines and Pharmaceutical Policy;
- Patient representatives;
- Health care insurers and investors.

With these criteria in hand, an initial longlist of candidate participants was drawn up. As the time window for recruitment was short, efforts to contact people on the longlist started already early in January 2016. The list was regularly revised and updated in the light of invitations accepted and declined. At the end of February 2016 the recruitment phase was closed. Appendix 1 includes the full list of contributors (interviewees and workshop participants) categorized according to the groups listed above.

The recruitment campaign was satisfactory in so far that high-level representatives and well-regarded experts for all the targeted groups could be persuaded to participate. Only one representative of a pharmaceutical company participated in the scenario development process. However, it was felt that the industry perspective was sufficiently broadly covered by a mix of experts in drug development, corporate innovation, health economics and health care investments.

2.3 Interviews

A total of 36 semi-structured and one-to-one interviews were held over an eight week period (mid-January to mid-March 2016) by three different analysts of the project team (Jo Goossens, Philippe Vandenbroeck and Rachel Wickert). The list of interviewees is included in Appendix 1. A limited set of questions relied on to guide the interview has been included in Appendix 2. Most interviews were held over the phone or via skype. The conversations lasted between 45 and 75 minutes. All interviews were recorded and a verbatim transcript was produced of all.

2.4 Analysis of the interviews

2.4.1 Approach

The aim of the analysis of the interview material was to pragmatically produce a content base to kick-start the scenario building process. Hence, a double focus was used to work through the material. First, we looked for a general framing of the drug pricing *problematique* as it emerged from interviewees' accounts. It was important to be able to corroborate the cautionary assessment of the project initiators that increasing prices for new drugs were a genuine problem. This would help to generate and sustain the requisite level of engagement of experts in the scenario development process.

Additionally from the interview material a set of 24 'building blocks' was identified. As explained earlier, the projected scenarios were conceptualized as 'typology scenarios' or 'solution scenarios'. Each scenario was expected to describe the rationale behind and working of an alternative drug development and pricing mechanism that would be more effective and cheaper in providing access to drugs for the people who need them. In the interviews experts suggested a series of functional elements that needed to be part of such alternative systems. Different constellations of building blocks would then provide a starting point for alternative scenarios.

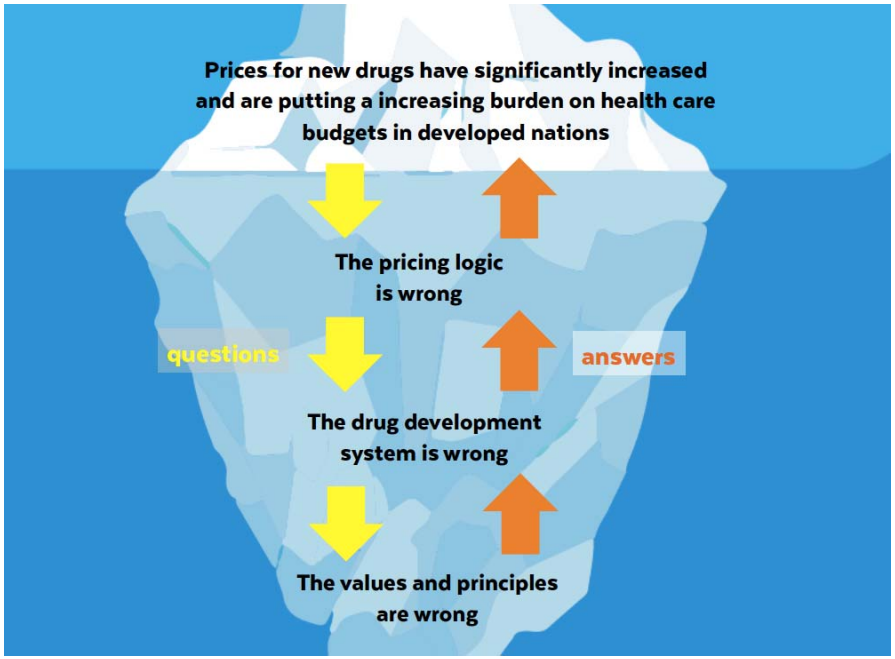
Given the short time available for analysis of the interviews the analysis was done in two collaborative sessions by members of the shiftN team. The results of the analysis were synthesized in a presentation that was shared with the participants at the start of the first scenario building workshop.

2.4.2 General framing of the drug pricing problematique

On the whole the experts subscribed to the cautionary assessment: prices for new drugs have significantly increased and are putting an increasing burden on health care budgets in developed nations. However, there were some statements that nuanced this general assessment:

- "Yes, prices for some drugs have gone up but a lot of drugs have become cheaper too. You cannot look at things that go up if you don't look at things that go down."
- "Yes, we might have a problem with the price of some drugs but it's not clear whether the price spent per health outcome is going up."
- "Well, we know that list prices for drugs have gone up but about the actual prices paid we don't know anything."

Figure 1 –Schematic of a metaphoric 'iceberg' that shows various perceptions of the drivers behind the challenge posed by increasing prices of new drugs.



While the overall challenge was acknowledged, the interviews revealed different assessments of the drivers behind this development. There was no consensus about whether high prices were the result of an ill-conceived pricing logic, a more encompassing failure of the whole drug development system, or even an outgrowth of the crooked values and principles that lie at the basis of the drug development system.

A synthetic systems diagram underscored this point (Figure 1). The diagram developed to visualize the (causal) interdependence between a limited number of factors that led to the increase in prices for new drugs and the increasing tension with the willingness to pay of governments and health insurers. In the diagram the elements were conceptualized as variables and blue or red arrows were used to show the dominant trend, up or down respectively.

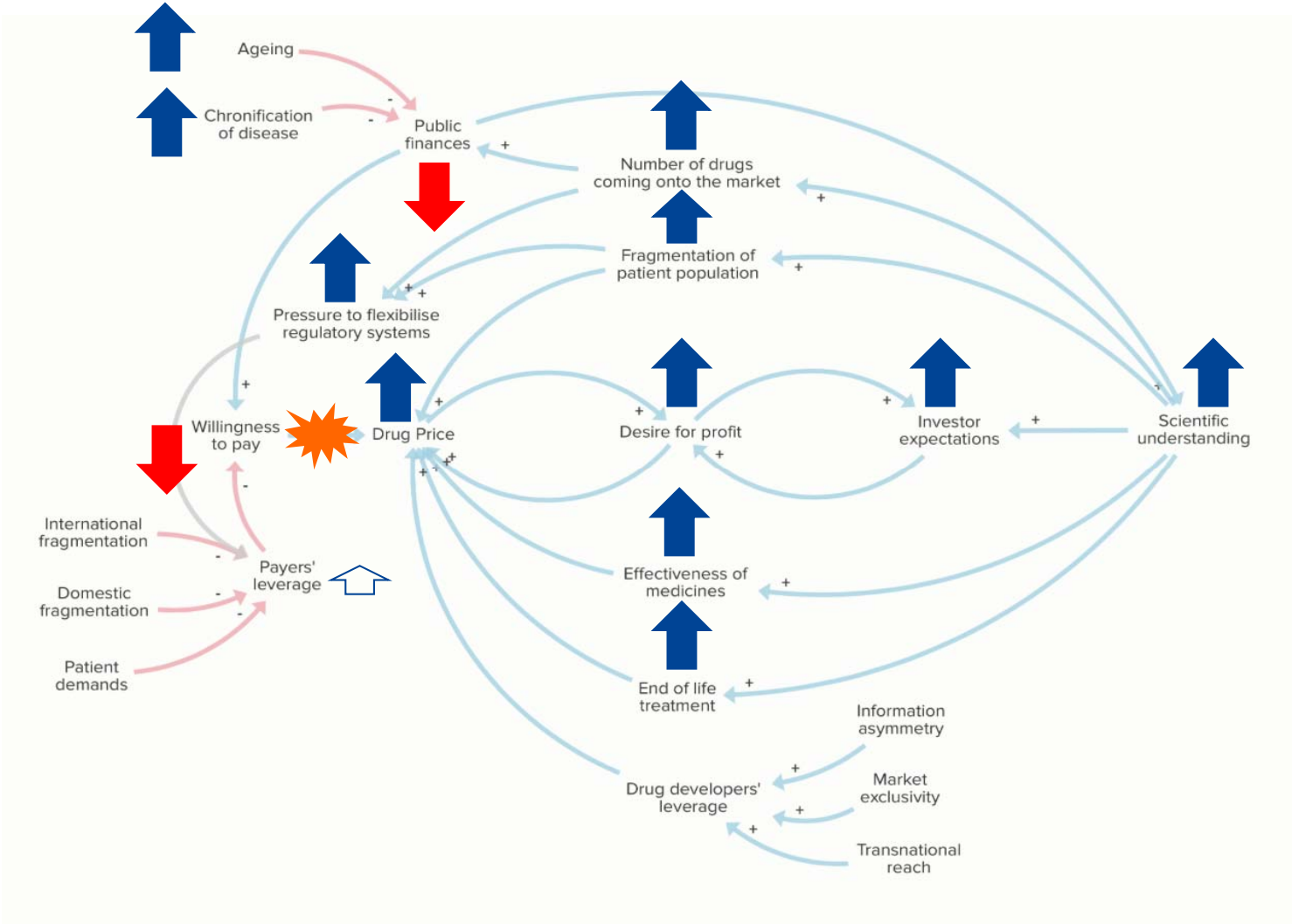
A number of driving forces were seen to contribute directly to increasing prices:

- increasing fragmentation of patient population;
- increasing desire for profit by drug developers;
- increasing effectiveness of medicines;
- increasing development of medicines for end of life treatments;
- high drug developers' leverage over price negotiations.

On the other hand, the willingness (and ability) to pay is coming under increasing pressure because public payers have to keep the system sustainable. With the demographic and epidemiological changes (ageing, chronification of disease), pressures on public finances, the large number of new drugs coming onto the market and payers' low leverage overall over price negotiations, this becomes increasingly difficult. The result is an increasing tension between rising prices and an eroding willingness to pay.

While this overall diagnostic picture reflected the aggregate view of the experts, it also revealed two dominant discourses amongst those interviewed: one group of experts saw the main trust in autonomous progress of science leading to more effective medicines and an increasing fragmentation of patient populations. These two factors can explain why prices for new drugs increase. Another group of experts emphasized much more ratcheting up of investor expectations and the financialization of the pharmaceutical industry. To them increasing prices were largely the result of an opportunistic business strategy to maximize the financial value captured from the market.

Figure 2 – Synthetic systems diagram showing the interdependence between drivers leading to an increasing tension between drug prices and buyers' willingness to pay



A final point made as part of this general framing was an assessment, based on interviewees' perceptions, of where this increasing tension would lead to if extrapolated to the future. Interviewees expressed a concern that the situation left unchecked would lead to a serious lose-lose-lose situation: value destruction on the side of industry, reduced opportunities for innovative therapies, drug shortages, loss of political capital for governmental decision-makers, and underserved patients. Clearly this provided a rationale to invest time and resources in finding creative solutions for this predicament.

2.4.3 *Building blocks for alternative drug development and pricing mechanisms*

A set of functional building blocks was distilled from the interview material. Different constellations of these elements were expected to form the basis for alternative solution scenarios. Obviously, a number of caveats were in order:

- Building blocks target a wide range leverage points. Political feasability, time and resources needed have not been made explicit.
- A single building block is unlikely to provide a way forward. One has to think in terms of functional clusters of elements.
- There is no consensus on the potential contribution of any of these building blocks.
- This synthetic survey is inevitably decontextualised and that it is vital to attend to the specific ways in which the building blocks are operationalised.

Below the 24 building blocks are listed, in the order with which they were communicated to the workshop participants. Each building block is described by a short headline and associated with an anonymized quote from the interviews to explain more clearly what is meant by it.

Building block 1 – Increase transparency in drug development and pricing

"*Transparency is for me the key. How much does it really cost to develop a drug? But we don't have that kind of transparency. It's quite funny how in the US the discussion about prices evolve. People are complaining about the list price, and now they're saying: nobody really pays the list price, because there are rebates and this and that. But it's all secret. So getting those data out in the open is an important element towards dismantling the power and TINA (There Is No Alternative) mindset that predominates today, both on pricing and on ways of doing R&D. So transparency is really key.*

Building block 2 – Introduce independent validation of clinical trials

"*The fact is that clinical trials are now done by the one actor that has vested interests in the outcome. This is a total conflict of interest. (...) So I think we should take it back to publically funded independent clinical researchers. You can request the industry to pay for it. I don't think the question is where the money should come from. But this is the place to have independent researchers who work in an open and transparent way, with new methodologies."*

Building block 3 – Increase payers' purchasing power

"*There's now this initiative between the Dutch, Belgian and Luxemburg authorities to work together to achieve more power in the market. I think this is the right way to do things. I believe that what all the other payers are playing is a stupid idea. Everybody thinks they're getting the best price, which they don't of course. So, doing things in a transparent way, together with other European countries, is probably a better way than sticking to these stupid rebates."*

Building block 4 – Centrally assess clinical value and price of new medicines

"The establishment of the EMA 20 years ago has saved member states of the EU intellectual and economical resources in assessing marketing authorisation applications, and ensured a homogeneous regulatory policy throughout the EU. HTA and price negotiation are left to national competent authorities. With the same aim to save effort, time and money and make the same medicines available and affordable in all the member states, these activities should be committed to a central European institution independent from the EMA. In the light of the assessment of the clinical (added) value of new medicines, this body should issue recommendations on their inclusion of national reimbursement schemes and negotiate their maximum reference

price for the whole EU, carrying to the negotiating table all the weight of half billion citizens, not just a few millions."

Building block 5 – Abandon external reference pricing

"*One of the big road blocks for me is the external price referencing. I have very big issues with it, mostly because it's putting your head in the sand. What the payers have done is to have a quick fix cost containment measure, which is: just look at the price people are paying; if it's lower than we just lower our pricing to the same extent. This has massive consequences which, I think, are not good for anyone, not for the industry, not for the payers. I think there's a couple of things we should decide on. Like do you think it's morally right that person from a poorer country, let's say Croatia or Cyprus, pays the same price as we? I think you'll find people at both sides of the spectrum. As a European, as a payer, we should ask ourselves this question. Do we believe that we should pay the same or do we believe that it's ok for us to support the poorer countries by paying a slightly higher price? I think there is something for and against each way, but if we don't make this decision, we'll never get to finding a solution."*

Building block 6 – Link drug prices to the value of the drug

"*I would go for an absolute value mechanism, which means that the economic spending on health care as a percentage of GDP is going to go up or down according to the quality of the technology that's put in front of us. The second thing is, once you've decided to pay absolute value, the very difficult question is: how do we define value? I think that's a very local decision. Belgium may define it differently than the Netherlands, Japan or the US. And how? You will have to make a choice about how you're going to do that mechanically. (...) Institutionally, you've got to vest your pricing mechanism in some body of authority. If it's about the choice between a certain amount of money and an additional year of life, you've got to invest an institution for that. I think NICE does that very well in the UK. The Federal Reserve of the US does that quite well for the economy and for money supply. My bias is that you're probably going to end up with that kind of institution."*

Building block 7 – Fund comparative effectiveness research

"*I think that one of the ways that governments can fund research that would enhance the competitive atmosphere and promote more rational drug pricing, would be by greater funding for comparative effectiveness research that would put products head to head, so that payers could make better decisions about which products are better than other products. This is not done as often as it should be done, as private actors have no incentive to do it, because they're concerned that their product would turn out worse."*

Building block 8 – Rely on uncertainty modulated flexible pricing

"I would introduce flexible pricing where I would say: if tomorrow new evidence shows us that your drug is better or worse than we thought, we will adjust that price, so I would not be locked into a high price. On the other hand, I would give the industry the opportunity to raise their price, if the outcomes are better than we had thought."

Building block 9 – Rely on contextual pricing

"*Right now we treat every patient as if they are average, but patients are not all average. Precision medicine is showing how we can harness the variability of patients, but our drug pricing mechanisms are very rigid and don't understand that there's a variation in patients and in drug effects for different patients subpopulations. I think we could do much better at having different pricing for different uses."*

Building block 10 – Subject new drugs to a requirement for therapeutic effectiveness

"*Today we do not request new medicines to show therapeutic advance at the regulatory level. If we would reintroduce the condition that only medicines that have been shown to produce any therapeutic benefit, whether it's safety, efficacy, cost effectiveness or whatever, get marketing approval, this would mean that actually 70% of the current R&D pipeline becomes redundant."*

Building block 11 – Prioritize reimbursements within a fixed macro-budgetary envelope

"What I would propose is that governments should actually make a budget for each year, saying "we're going to spend one or two billion for new interventions in health care. And all these new interventions will be lined up at the beginning of the year and we can choose what we're going to pay for". That means that there's some kind of competition going on between a number of new interventions. So if you want to be in, you need to make sure that you're attractive enough to be actually selected in the priority list of new interventions that have to be taken up in the health care system. (...) I think this system will in the end drive prices down, because if you want to fit in as much health care as possible in a limited budget, all sorts of suppliers will try to fit in and lower the prices."

Building block 12 – Engage in early dialog to collaboratively assess effectiveness and pricing

"*There are HTA early dialogues with companies that move from phase 2 to phase 3. Agencies suggest what end points need to be collected in order to have a better chance for reimbursement. My reflection is: why wouldn't we at this point also discuss the future price of the drug, because the company is about to make a huge investment? Why not take the opportunity to collect not only the end points and comparators, but also what price could be justified for the benefit that you will yield? Because we already have more or less an idea of what the expected benefit of the molecule will be, given the results of phase 2."*

Building block 13 – Engage in drug development PPPs

"*One mechanism is to share the risk. What I call the shared risk model. In other words, you invest in something with the company. Basically, you share as a government the investment in R&D. So you take the risk with the innovator and by sharing the risk, you reduce the risk. So it's a risk reduction model. That way, you keep costs down. (...) You share your risk and keep the cost down, so none of the parties is taking the risk on its own, providing one of those partners is a non-profit partner, and sometimes this could be governments."*

Building block 14 – Acknowledge the contribution of publically financed research in drug prices

"I think that if there was greater recognition of the contribution of publically funded science to drug development and a clearer connection between products that arise from publically funded science and their prices or the access to them, or greater compensation back into the research system, for products based on publically financed science, I think that that would be more equitable. Today, a lot of the publically funded science is captured by and turned into private enrichment."

Building block 15 – Decouple R&D markets from sales markets

"*I would create the largest horizon scanning system there is, where I would know about and keep track of all the pre-clinical phase 2–phase 4 trials and decisions by institutions about what to reimburse or not. So I would know what's being developed, and I would be looking pro-actively at what's happening and where the gaps are. For instance, I can see that there are no investments in malaria, there's no more investment in diabetes or antibiotics. And so, before the problem arises, you start targeting it. "We're going to have a problem in ten years' time, because there are no anti-microbial drugs being developed". I'm sure that, if we had known this ten years ago, we would not have had a problem with antibiotics, but payers are absolutely not aware of what's going to happen.*

So that's my first thing. I would create knowledge, so people can find whether something is being invested in. If I would see that the industry is not going to invest into something, we should put our heads together with countries worldwide, put some money in and buy off the patents as soon as they're through phase 2, and say to the company: you've invested 200 million, I pay you 400 million. Then it becomes a generic and everyone can continue with further trials, but you're not paying the patents anymore."

Building block 16 – Support a competitive, transparent research infrastructure that deprioritizes ownership

"*The bottom line, as I see it, is the secrecy of the research producers, which leads to inefficiency. I prefer research to be fully open source, where everybody shares everything and anybody can participate. If you abandon secrecy, then you also abandon the ability to protect intellectual property.*

This is the essential feature of open source. You allow anybody to do anything and you disclose things immediately.

There are certain areas where open source is essentially a no brainer, where there is no money to be made. And these are the tropical diseases, malaria and to some extent tropical diseases in general. If you extend the argument and you come across things like Alzheimers, where the pipeline is there, I think we spent 24 billion dollar in the last decade in this area, and only one drug has reached the market, and it's not even a very good one. Patient care costs are so enormous that we simply can't afford to give all these people a really expensive drug. It's just not going to work. The insurance industry will not be able to handle it if we suddenly have millions of people needing a pill that costs a hundred thousand dollars. From a government point of view, you'll say: this is so expensive that we as a government or a collection of governments need to step in and solve this problem, otherwise we're going to bankrupt ourselves."

Building block 17 – (Re-)introduce compulsory licensing

"*Compulsory licensing has worked very well in countries where it has been deployed. It doesn't work because if governments don't use it does not work. Here is a very clear example of a mechanism that a government has at its disposal that could be used but is not being used. You could argue that in European countries that when companies price the product at a level where the authorities say that it is an effective medicine but we cannot afford it (...) they abuse their market position. In which case a government should intervene. It could intervene by issuing a compulsory license or by issuing a government use license and try to procure the product somewhere else. Those are all mechanisms that are highly effective if they are deployed. They have not been deployed recently in Europe. In the past it was common practice. But recently this has not been used."*

Building block 18 – Reduce demand for drugs through prevention

"*We know that a lot of diseases that we have to pay for and constitute very heavy burden are related to lifestyle choices and other issues that could be very effectively treated by prevention. (...) we waste a lot of resources and we don't look at other things that would be truly cost-containing. The mindset, logic, has to change."*

Building block 19 – Develop an ethically defensible regulation for public goods

"*Shifting back drugs in the direction of a public good: for me, this is the fundamental battle in the very long term. It has to do with a ripening of the moral values in humankind on a global scale. As we have seen, during the last century, an evolution of new moral standards for war prisoners, for chemical warfare, trade unions and labour protection. We should have a similar evolution to gain new insights, new moral standards for the drug business, drinking water business, education business."*

Building block 20 – Developed a tiered pricing logic on a pedestal of true development costs

"*Things start with a discussion on the cost: what have been your different costs, what are going to be the different costs? And based on that, they add 20% on average of the profit of the sector. That gives you the first layer of the price. Then you do a value assessment, based on certain criteria, as always. And then, it has a multiplying factor between ten and one hundred percent. This is where you get the reward for the risk and innovation and for the real high value or not. And on top of that, you have another 10% if it's introduced first in EU. And we could also have a final ten percent if it's an orphan drug (...). This is how we would see the cost construction: a multiplying factor between ten and hundred percent according to your assessment, then something to attract investment, especially for stronger needs, where there is nothing yet."*

Building block 21 – Develop foresight capacity

"*I would create the largest horizon scanning system there is, where I would know about and keep track of all the pre-clinical phase 2–phase 4 trials and decisions by institutions about what to reimburse or not. So I would know what's being developed, and I would be looking pro-actively at what's happening and where the gaps are. For instance, I can see that there are no investments in malaria, there's no more investment in diabetes or antibiotics. And so, before the problem arises, you start targeting it. "We're going to have a problem in ten years' time, because there are no anti-microbial drugs being developed". I'm sure that, if we had known this ten years ago, we would not have had a problem with antibiotics, but payers are absolutely not aware of what's going to happen."*

Building block 22 – Align drug development with clear health priorities

"I would look to other places where governments or companies have been very clear about what they need for outcomes and that drives back into what their initial scientific requirements are. So we do that very well with military products, we do that very well with space exploration products, we do it reasonable well with big physics products, like the CERN-complex in Switzerland, when you have the end in mind and go back to the beginning: this is what we want and this is what we can afford to pay."

Building block 23 – Educate and empower patient/citizens

"Clearly patients are at the centre of all of this. If we don't know what they want and we don't know what matters to them we will be continuing to develop drugs that are not useful. And this is one of the problems with the cancer drug development at the moment. What we focus on is trying to target changes on a tumour on a scan and not for example on impact on the quality of life. So that has got to change, I think we have to work out a much better way of interfacing not only with patients, here I am not only talking about patients having a specific disease, but the more broad community of consumers who may not have a particular disease but may have a view on what that patient group should have in term of access to treatment. So we could think about systematic ways that governments can support patients that meant that they don't have to get funding from industry."

Building block 24 – Create clarity on what our societies expect from our health care systems

"*What is it that we really need? Are we believing that medicine will progress more and more, so that eventually we will have eternal life? What is it that we are striving for? It's a societal debate that we didn't have so far. What is that we expect from tomorrow's medicine? (…) But there's no real questioning about: what is good health about? What are we trying to achieve with our medical research?*"

2.5 The scenario development process

The scenario development process essentially was structured in four steps:

1. Refinement of the purpose served by the projected drug development and pricing systems;
2. Refinement of the collection of functional building blocks;
3. Development of seed scenarios as clusters of building blocks;
4. Elaboration and consolidation of scenarios.

The work was performed by experts in two 1,5 day workshops (in Amsterdam, on 17-18 March 2016 and 21-22 April 2016, respectively) guided by members of the shiftN team. The first workshop focused on the first three steps. An interim report was produced and sent to all participants. The project team streamlined the workshop output in preparation for the second session that was then devoted to an elaboration of the seed scenarios into more fully developed scenarios.

3 RESULTS

3.1 Results from the first scenario building workshop

3.1.1 Refinement of the purpose served by the projected drug development and pricing system

It was felt necessary to precisely articulate the purpose that needed to be served by the drug development and pricing mechanism described in the projected scenarios. This purpose was expressed as follows.

To provide patients sustained access to the safe and effective drugs they need, with particular attention to the role of pricing.

3.1.2 Refinement of the collection of functional building blocks

Experts debated, amended and expanded the original collection of building blocks. The list of revised building blocks turned out as follows. Items in italic were reworded compared to the original phrasing. Five elements were added, identified by capital letters A to E.

1. Increase transparency in drug development cost, priority setting & pricing (+ B)
2. Introduce independent validation of clinical trials.
3. Increase payers' purchasing power.
4. Centrally assess clinical value and price of new medicines.
5. Abandon international reference pricing.
6. Adopt value-based pricing based on principled negotiation processes.
7. Fund comparative effectiveness research.
8. Rely on 'uncertainty modulated' flexible pricing.
9. Rely on indication-specific pricing (different prices for different uses).
10. Subject new drugs to a requirement for therapeutic effectiveness (avoid surrogate endpoints).
11. Prioritise reimbursements within a fixed macro-budgetary envelope (portfolio management of health care ambitions, e.g. MOCA).
12. Engage in early dialogue (binding or not) to collaboratively assess effectiveness and pricing binding.
13. Engage in drug development PPPs.
14. Value the contribution of publically financed research in drug prices.
15. Find alternative ways to compensate R&D efforts that allow to modulate exclusivity rights at the market access stage (decoupling).
16. Support a competitive, transparent research infrastructure that de-prioritizes ownership.
17. Introduce compulsory licensing.
18. Reduce demand for drugs through prevention.
19. Refocus and revamp international treaties in favour of public health and equity.
20. Develop a tiered pricing logic on a pedestal of true development costs.
21. Develop foresight capacity.
22. Align drug development with clear health priorities.
23. Educate and empower patient/citizens and preserve their independence from commercial interests.
24. Create clarity on what our societies expect from our health systems.

A Monitor real life use with focus on evidence and guidelines development.

B Create transparency on payers' priorities and willingness to pay.

C Preserve independence from commercial interests of institutions, regulators, and health professionals dealing with drug development, pricing and purchases.

D Ensure a fair competitive environment for generics (e.g. combat anti-competitive practices).

E Back up post-authorization real-life use monitoring of accelerated market evaluation with un-biased evaluation of safety and efficacy trials.

3.1.3 Development of scenario seeds

Experts gathered in four subgroups to develop seed scenarios starting from the revised collection of building blocks. The results of these deliberations have been more fully documented in Appendix 3.

Overall, eight seed scenarios were developed:

- Subgroup 1 offered three seeds: 1.1 ('countervailing force'), 1.2 ('open source scenario') and 1.3 ('fixed-budget scenario');
- Subgroup 2 offered one seed: 2.1 ('parallel drug development');
- Subgroup 3 offered two seeds: 3.1 ('alignment of drug development with public health needs') and 3.2 ('value-based pricing and cost+');
- Subgroup 4 offered two seeds: 4.1 ('non-exclusivity and new incentives') and 4.2 ('adaptive licensing').

Four of these were more extensively developed (1.1, 2.1, 3.1 and 4.1) and incorporated 8-15 elements, several of which were shared amongst the four seeds. The remaining four remained sketchy and pivoted around one or two key ideas. An overview table shows how the seeds scenarios were composed in terms of building blocks.

Table 1 – Overview of composition of initial set of seed scenarios (workshop 1) as a function of the revised set of building blocks

Building block		Seed Scenarios							
		1.1	1.2	1.3	2.1	3.1	3.2	4.1	4.2
1	Increase transparency in drug development cost	X				X	X		
2	Introduce independent validation of clinical trials	X			X	X		X	
3	Increase payers' purchasing power								
4	Centrally assess clinical value and price of new medicines	X					X		
5	Abandon external reference pricing								
6	Link drug prices to the value of the drug							X	
7	Fund comparative effectiveness research				X	X		X	
8	Rely on uncertainty modulated flexible pricing								X
9	Rely on contextual pricing								
10	Subject new drugs to a requirement for therapeutic effectiveness				X	X		X	
11	Prioritize reimbursements within a fixed macro-budgetary envelope			X					
12	Engage in early dialog to collaboratively assess effectiveness and pricing binding	X							X
13	Engage in drug development PPPs								
14	Acknowledge the contribution of publically financed research in drug prices	X	X						
15	Find alternative ways to compensate R&D efforts that allow to modulate exclusivity rights at the market access stage (decoupling)	X			X	X		X	

16	Support a competitive research infrastructure that deprioritizes ownership		X		X	X		X		
17	Introduce compulsory licensing									
18	Reduce demand for drugs through prevention									
19	Refocus international treaties in favour of public health and equity	X				X				
20	Develop a tiered pricing logic on a pedestal of true development costs						X			
21	Develop foresight capacity	X			X			X		
22	Align drug development with clear health priorities	X		X	X	X		X		
23	Educate and empower patients/citizens	X						X		
24	Create clarity on what our societies demand from health care systems	X		X	X			X		
A	Monitor real life use with focus on evidence and guidelines development								X	
B	Create transparency on payers' priorities and willingness to pay	X					X			
C	Preserve independence from commercial interests of institutions, regulators, and health professionals dealing with drug development, pricing and purchases							X	X	
D	Ensure a fair competitive environment for generics									
E	Back up post-authorization real-life use monitoring of accelerated market evaluation with un-biased evaluation of safety and efficacy trials							X		

Looking more closely at the overlap in composition in the scenario that was more elaborated by each subgroup the following observations could be made:

- Building blocks shared by all four versions of the scenario:
  - 2 Introduce independent validation of clinical trials.
  - 15 Find alternative ways to compensate R&D efforts that allow to modulate exclusivity rights at the market access stage (decoupling).
  - 22 Align drug development with clear health priorities.
- Building blocks shared by three of four versions:
  - 7 Fund comparative effectiveness research.
  - 10 Subject new drugs to a requirement for therapeutic effectiveness
  - 16 Support a competitive, transparent research infrastructure that de-prioritizes ownership.
  - 21 Develop foresight capacity.
  - 24 Create clarity on what our societies expect from our health systems.

So we might conclude that several features are seen to be central to any future drug development and pricing mechanism: transparency, effectiveness, alignment of drug development with public health priorities, alternative IP management and rewards.

In addition there were a number of scenario seeds that relied on one or two key building blocks:

- Scenario that revolves around building block 11: "prioritise reimbursements within a fixed macro-budgetary envelope (portfolio management of health care ambitions, e.g. MOCA)."
- Scenario that revolves around building blocks 8 and 12:"engage in early dialogue (binding or not) to collaboratively assess effectiveness and pricing" and "rely on 'uncertainty modulated' flexible pricing."
- Scenario that revolves around building block 20: "develop a tiered pricing logic on a pedestal of true development costs (cost+)."

Also noteworthy is that a number of building blocks did not find a place in any of the seed scenarios:

- 5 Abandon international reference pricing.
- 9 Rely on indication-specific pricing (different prices for different uses).
- 13 Engage in drug development PPPs.
- 17 Introduce compulsory licensing.
- 18 Reduce demand for drugs through prevention.

3.2 Results from the second scenario building workshop

An initial part of the second workshop was devoted to an exploratory discussion to expand on the results of the March session. Four subgroups were formed, each with a mandate to expand a different seed scenario. As already discussed the first workshop resulted in 8 seeds overall, four of which could potentially be clustered around a set of core ideas, and four others which revolved around one or two building blocks. Subgroups were asked to focus on these embryonic scenarios to see whether they were strong and interesting enough to be expanded. One subgroup of delegates was formed with a request to come up with a seed scenario that was outside of the scope of the discussion during the March session. This was meant to check whether any of the experts' ideas had been left unexplored. Finally, it was decided very early on to not further investigate a scenario seed that revolved around a 'cost plus' reward model but to focus on the possibilities of private-public partnerships instead. This was one of the building blocks that had not been included in any of the seeds in the first round.

Eventually four subgroups were formed to engage in a short exploratory exercise:

- A subgroup to further develop a seed scenario that revolved around building block 11: "prioritise reimbursements within a fixed macro-budgetary envelope (portfolio management of health care ambitions, e.g. MOCA)."
- A subgroup to further develop a seed scenario that revolves around building blocks 8 and 12:"engage in early dialogue (binding or not) to collaboratively assess effectiveness and pricing" and "rely on 'uncertainty modulated' flexible pricing."

- A subgroup to develop a seed scenario that revolves around building block 9: “Engage in drug development PPPs”.
- A subgroup with a request to develop a new seed scenario.

The group tasked with developing a new seed scenario proposed a ‘radical public health scenario’ that would turn drug development in a public enterprise focused on generating solutions (drugs or other types of interventions or technologies) for unmet health-related needs.

After these discussions all seeds scenarios generated hitherto were reviewed and a final set of four seeds was proposed for further development:

- A seed scenario that revolved around needs-oriented, contract-governed PPPs.
- A seed scenario that revolved around the development of a parallel drug development track (seed seed scenario 2.1 from the first workshop, Table 1).
- A seed scenario that revolved around the establishment of a ‘public fund for affordable drugs’. This seed connected to seed scenario 1.1 from the first workshop (see Table 1).
- A seed scenario that envisaged the development of drug development as a public enterprise.

Groups of experts spent more than half a day on the development of their scenarios. They were asked to develop a coherent narrative and timeline. At this point the requirement to connect the scenario logic to the set of building blocks was loosened. Groups were free to refer to them as they saw fit. A final, extensive plenary feedback and discussion session brought the workshop to an end.

Immediately after the workshop the output – both in written and recorded form – was processed by the shiftN team. Given a tight and unmovable deadline the draft scenarios contributed by the groups were transcribed into more polished narratives. These were reviewed by the project team members of KCE and ZIN and subsequently shared with the contributing experts, who had one week to propose improvements and amendments. This input was the basis for another iteration, leading to a final version of the scenarios.

The scenarios have been reported in a summary report (‘brochure’) that aims at a wide readership (KCE/ZIN, 2016). Below only a shortened description is provided.

3.2.1 Scenario 1 – Needs-oriented Public-Private Partnerships

Public actors and drug developers are tackling public health priorities in vigorous and pragmatic partnerships. The public actor identifies indications representing high public health needs; specifies criteria for the performance levels of drugs to be developed for those indications; and indicates his willingness to pay. Through procurements with enforceable contractual commitments, the public actor enters into a partnership with drug developers to find solutions for these needs. Developers are prepared to enter into the partnership and to give price concessions for a pre-negotiated fixed agreement on price and volume, and speedier access to market, which reduces their development risk. This drug development and pricing model is close to existing governmental procurement practices in research intensive areas such as public transport, defence and space exploration.

3.2.2 Scenario 2 – Parallel Drug Development Track

EU member states set up a parallel, not-for-profit drug development track that exists alongside, but independent of, the pharmaceutical and biotechnological industry. The aim of the parallel track is to develop cheaper drugs without compromising safety and effectiveness. After having made up an inventory of the public health gaps and priorities in healthcare, EU member state authorities ask leading public research institutes which discoveries, assets, tools and capabilities they possess in order to develop solutions addressing (some of) the needs that were identified. Starting from the match between demand and available expertise, coalitions are built between these (not-for-profit) research institutes, payers, authorities and patient organisations. All these partners make the commitment to participate in an open and transparent way in clinical research projects. Intellectual property (IP) rights are acquired early on in the development process by the partners of the consortium, and ownership is shared. Alternatively, the parallel research infrastructure can completely de-prioritise ownership, i.e. inventions and developments in the parallel track are not protected and are in the public domain.

3.2.3 Scenario 3 – Pay for Patents

A consortium of European countries has joined forces and has established a 'Public Fund for Affordable Drugs'. Each of the participating countries deposits a fixed annual percentage of what they currently spend on drugs into the Fund. Private payers (including insurance companies) can also join the Fund.

The Fund continuously screens the research market for 'interesting' drugs that are being developed in phase II or in phase III for indications with clear health priorities. The Fund buys off the patents from developers, conducts or commissions the last phases of research in public research institutes, or subcontracts to private partners (but then with strict public oversight), and guides the submission process for market authorisation. Because the drug is then put on the market at a relatively low price, this generates substantial savings for the public payer. Once the system is functioning 'at cruising speed', these savings can (partly) serve to replenish the Fund. The 'Pay for Patents' model delinks research and development from manufacturing and sales. The prices decrease because the partners in the Fund consider medicines as public goods, which should not be financed through monopoly prices. Hence, once the patent is owned by the public sector, after a successful development and authorisation trajectory, the rights to produce, distribute and sell the drug can be licenced to manufacturers and distributors that provide the best deal in terms of quality, safety, and accessibility for the lowest cost. As a rule, various private partners compete with each other, with the result that 'new drugs enter the market at generic prices'.

3.2.4 Scenario 4 – Public Good from A to Z

Drug development is essentially a public enterprise, and has been radically reoriented from serving private profits towards serving the public interest and the needs of patients. In a drug development system that is essentially a public enterprise, private drug companies still have a role, albeit with a completely different business model. They mainly manufacture drugs and deliver services to the public provider on a competitive basis. With drugs and other health technologies essentially public goods, there is no role for patents or monopolistic prices.

Patients and public health providers, not corporations, choose which unmet needs research should address. Public authorities regularly publish lists of research priorities, based on objectively established and patient-informed unmet medical needs. Governments organise and fund that research through a variety of mechanisms, including requests for proposals based on well-defined targets that any research team, public or private, can compete for, or milestone compensation, and active management of the innovation process. By paying directly for R&D and active management of the drug development pipeline, nations and healthcare systems pay much less than the patent-protected prices of the past. Ultimately, drug prices are set on the basis of the real costs of manufacturing, quality control and distribution, which are decoupled from R&D.

4 CONCLUSION

The four scenarios offer possible evolutionary pathways of the current drug development and pricing system. They all rest on the principle that being entitled to medical care is a basic human right. Consequently, they project a range of futures in which the development of new medicines is emphatically guided by the public interest.

In recent years, many of the conceptual building blocks of these scenarios have been discussed in various fora. Here, they are brought together in a few shared frameworks. The scenarios should not be seen as mutually exclusive. It is not inconceivable that a future will emerge in which public procurement-guided partnerships, state-sponsored drug development efforts and decoupling mechanisms appear side by side. The 'Public Good from A to Z' future should arguably be seen as extending to their limit some of the principles at work in the other scenarios.

An inescapable conclusion of this work is that drug development and pricing will have to go through a significant transition to respond to 21st century public health challenges. Informed by new rationales to weigh the risks and benefits of investments in health improvements, the relationship between patients, payers, and drug developers will change. Conventional ways of dealing with intellectual property rights will have to be revised for medicines, which, after all, are not consumer goods but products with a public goods character. Appropriate incentives, skills and attitudes will render the drug development and pricing system more responsive, accountable … and responsible. Foresight and stewardship are poised to become key competencies for public authorities. Increased transparency and an unwavering commitment to good governance are essential ingredients of all futures imagined in this project.

APPENDICES

APPENDIX 1. CONTRIBUTORS TO THE DRUG PRICING SCENARIOS PROJECT

This is a list of the expert contributors to the scenario development process. Names labelled with a (*) made themselves available for an interview but did not participate in the scenario workshops.

Organizers (KCE/ZIN)

- Irina Cleemput (KCE, BE)
- Lydia de Heij (Zorginstituut Nederland, NL)
- Frank Hulstaert (KCE, BE)
- Raf Mertens (KCE, BE)
- Martin van der Graaff (Zorginstituut Nederland, NL)

Belgian and Dutch payers

- Francis Arickx (RIZIV – INAMI, BE)
- Ri De Ridder (RIZIV – INAMI, BE)
- Eveline Klein Lankhorst (Ministerie van Volksgezondheid, Welzijn en Sport, NL)

Regulators, Public authorities

- Hans-Georg Eichler (European Medicines Agency, UK)
- Suzanne Hill (World Health Organisation, CH) (*)
- Hugo Hurts (College ter Beoordeling van Geneesmiddelen, NL)
- Valérie Paris (L'Organisation de coopération et de développement économiques – Organisation for Economic Co-operation and Development)

Experts in the area of Intellectual Property Rights

- Isabelle Huys (Katholieke Universiteit Leuven, BE)
- Aaron Kesselheim (Harvard Medical School, US) (*)
- Ellen 't Hoen (Universitair Medisch Centrum Groningen, NL)

Experts in the area of Drug Development

- Peter Bach (Memorial Sloan Kettering Cancer Centre, NY - VS)
- Jean-Jacques Cassiman (Katholieke Universiteit Leuven, BE) (*)
- Silvio Garattini (Istituto di Ricerche Farmacologiche Mario Negri, IT)
- Peter Gøtzsche (Nordic Cochrane Centre, DK)
- Denis Lacombe (European Organisation for Research and Treatment of Cancer, BE)
- Matt Todd (University of Sidney, AUS) (*)

Experts in the area of Corporate Innovation

- Mark Trusheim (Massachusetts Institute of Technology, US)
- Walter Van Dyck (Vlerick Business School, BE)

Experts in the area of Health Economics

- Panos Kanavos (London School of Economics, UK)
- Joan Rovira (University of Barcelona, ES)

Experts in the area of Business Ethics

- Donald W. Light (Princeton University NJ – VS)

Pharmaceutical industry

- Koen Torfs (Janssen Pharmaceutical Companies of Johnson & Johnson, DE)

Experts on consumer protection, access to medicines and pharmaceutical policy

- Teresa Leonardo Alves (Universiteit Utrecht / WHO Collaborating Centre for Pharmaceutical Policy and Regulation, NL)
- Sharon Batt (Dalhousie University, Halifax, NS - CA)
- Marcel Canoy (Autoriteit Consument & Markt / Erasmus School of Accounting and Assurance / Lonkanker Nederland, NL)
- David Hammerstein (Commons Network, ES)
- Raj Long (Bill & Melinda Gates Foundation, VS)
- Donna Messner (Center for Medical Technology Policy, US) (*)
- Yannis Natsis (European Public Health Alliance, BE)

- Els Torreele (Open Society Foundations, NY – US)
- Sean Tunis (Center for Medical Technology Policy, US) (*)

Patient representatives

- Yann Le Cam (Eurordis, FR)
- Cor Oosterwijk (Vereniging Samenwerkende Ouder- en Patiëntenorganisaties voor Zeldzame en Genetische aandoeningen, NL)
- Jean-Louis Roux (EURORDIS, BE)

Health care insurers and investors

- Richard Evans (Sector Sovereign, US) (*)
- Stijn Vanacker (Robeco, NL)

APPENDIX 2. GUIDING QUESTIONS FOR EXPERT INTERVIEW

- This project starts from the observation that prices for innovative drugs have consistently increased over the last decade. Do you support this observation? What explains this development? If this development is left to itself where will it lead to?
- Is there such a thing as a 'drug pricing mechanism'? Can we conceptually demarcate it? What drivers and actors play a key role in it?
- If you could design a drug pricing mechanism from scratch, how would you do it? What innovative approaches and initiatives out there would you rely on?
- How would you measure the performance of a drug pricing mechanism? What trade-offs are to be considered?
- What do you hope will this scenario project achieve?

APPENDIX 3. SEED SCENARIOS DEVELOPED DURING SCENARIO BUILDING FIRST WORKSHOP

Appendix 3.1. SUBGROUP 1

Seed scenario 1.1

Creating countervailing power

As a starting point the group used the building blocks

24. Create clarity on what our societies expect from our health systems.

22. Align drug development with clear health priorities.

19. Refocus and revamp international treaties in favour of public health and equity.

These form the general principles of a new health care system. Together the three blocks describe 'what we value as a society' and 'what we want to invest in'. Ideally these priorities should be discussed and decided upon on a global scale, i.e. the UN or WHO. Likely, this would not work in practice. Therefore, the EU should be the minimal scale to define these priorities.

How do we get there?

Transparency and insight: An important group of building blocks has to do with creating transparency and increasing insight. All parties involved should 'open up their books'. Building blocks to achieve this are:

1 *Increase transparency in drug development cost, priority setting & pricing*

B *Create transparency on payers' priorities and willingness to pay.*

21 *Develop foresight capacity*

12 *Engage in early dialogue (binding or not) to collaboratively assess effectiveness and pricing.*

Level playing field (between all parties): the second phase is to create a level playing field and develop instruments to generate countervailing power, i.e. also give the patients a voice in the system.

Building blocks are:

23 *Educate and empower patient/citizens and preserve their independence from commercial interests.*

In terms of concrete actions, the following building block needs to be activated:

2 *Introduce independent validation of clinical trials.*

4 *Centrally assess clinical value and price of new medicines.*

14 *Value the contribution of publically financed research in drug prices.*

15 *Find alternative ways to compensate R&D efforts that allow modulating exclusivity rights at the market access stage (decoupling). An example of 15 is 17 Introduce compulsory licensing*

The idea of decoupling (15) is to pay off patents after clinical phase 2 with a fair reward for inventors (who should refocus their efforts on research and inventions, and less on 'profit making'). After the research and development phase, the new drug comes in a more 'general phase' (i.e. manufacturing, distribution, …) with competition. Since the patents are now owned by the public sector, the rights to produce, distribute and sell can be licensed to organizations that provide the best deal in terms of quality, safety, accessibility, … for the lowest cost.

Measures of performance

The scenario would lead to a concept that the payer would only pay for the drugs that work and are efficient ('the good things' and the 'real innovation'). However, that might be at lower or higher prices (matter of internal discussion in the group) compared to the current prices. There was also disagreement within the group whether in this scenario the return on investment could be high enough for inventors and industry. The risk could be that innovation would stall.

For a number of participants it is counterintuitive to see how this scenario might be effectively implemented knowing how the industry values its products currently (and which is in line with the current legislative framework of patents and licensing habits). The industry also compensates the investment loss from failures by making high profits on their successes.

Others argue that currently billions and billions are spent to pay for unproductive medicines. That money would be freed and could be used for

true innovation. This is one of the elements to make this scenario commercially viable. Of course, a number of practical issues need to be resolved: intelligent criteria and scales should be drafted, but these are a matter of political implementation.

Discussion

The 'countervailing power' scenario is seen as a radical scenario with a total system change. Two key functional elements seem to emerge: the priority setting and the decoupling. To let these two core elements interplay in a functionally viable way, other building block like transparency, independence, and innovation are ensuring mechanisms.

Seed scenario 1.2

Open source

This scenario was not fully developed by the subgroup. The setting is a not for profit setting. The basic idea is that academic freedom and creativity really (should) drive innovation. Innovation in this scenario should be 'salary based', so the current bad incentives are less prominent present. However, to become feasible, 'open source' needs a combination of intrinsically salary paid university employees who are curiosity driven coupled with not for profit pharmaceutical companies.

The building blocks to make this transformation are:

14 Value the contribution of publically financed research in drug prices.

16 Support a competitive, transparent research infrastructure that de-prioritizes ownership.

Seed scenario 1.3

Win-win scenario

This scenario is based on more collaboration between stakeholders. Building blocks are

24 Create clarity on what our societies expect from our health systems

22 Align drug development with clear health priorities

11 Prioritize reimbursements within a fixed macro-budgetary envelope

The setting is a dialogue environment with respect for each other's positions. This is a less aspirational scenario and counts on the goodwill of the current stakeholders to make necessary adaptations within the current system and legislation.

Appendix 3.2. SUBGROUP 2

Seed scenario 2.1

The parallel drug development track

This group proposes a parallel, not-for-profit drug development track, that will exist alongside, but independent of the existing pharmaceutical and biotechnological industry. The aim of the third track is to develop drugs in a more cost effective way.

On the one hand, this parallel track will fill in the gaps that the current industry is not interested in (i.e. orphan medicines, malaria, neglected diseases, …). On the other hand it will also develop drugs in competition with the 'for-profit' industry. However, the parallel track will develop these drugs without the side effect of high drug prices by avoiding extra costs for sales forces, marketing expenses, high salaries for CEOs and management, etc. The scenario contains the following building blocks:

First, society has to *create clarity on what it expects from the health system (building block 24)*

Secondly, it makes an inventory of needs and what R&D is able to deliver.

The following building blocks are involved:

21 Develop foresight capacity.

Find out what science can deliver? (Extra Building block)

22 Align drug development with clear health priorities.

The authorities make an inventory of the health gaps, the needs that are not addressed, or the needs that are currently addressed in an insufficient or improper way. Further, a broad enquiry is made on 'what science can deliver'. Every innovative development is limited and constraint by the capabilities of science and technology. Leading institutes like MIT, Academic Medical Centres, Research Institutes, and Universities will be asked which assets, tools and capabilities they have available to develop in the next 10 to 20 years solutions addressing (some of) the medical needs which were identified in the previous phase.

Starting from a matching between demand and offer, coalitions are built between (not-for-profit) research institutes, payers, authorities and patient organisations. All these partners make the commitment that they want to participate (in an open way) in clinical research projects in a parallel development track.

Following cases were given as examples showing the such coalitions can work:

- Several health insurers already have in place databases and software systems to perform their own clinical studies in silico.
- Online patient platforms (PatientsLikeMe) or independent patient's organisations are willing to do their own clinical studies

Funding

Creative funding schemes with alternative ways to *compensate R&D efforts should be worked out (building block 15)*. They can consist of upfront payments for development, instead of payment for drug use. But also sources like crowd funding, social bonds, and other financing options can be addressed.

IP rights

IP rights could be acquired early on in the development process (a form of *decoupling – 15*) or the *parallel, competitive, transparent research infrastructure completely de-prioritizes ownership (16)* by releasing IP rights, i.e. inventions and developments are not protected in the parallel track. Instead of insisting on doing the whole development themselves, the consortia encourage other partners (also from industry) to pick up promising results at any stage and build further on these. The main concern of the consortia (and the health system) is the outcome (the product or the solution for an affordable price), not the entity that develops it. In that perspective ownership becomes irrelevant, as long as the goals are reached. Organizations like EORTC prove that efficient drug development is possible in a more cost effective way compared to the industry. These organizations count on voluntary collaboration from hospitals, organizations and individuals.

Old and new co-exist

A parallel drug development track provides health authorities with a 'try out' option if it believes that for certain indications or unmet needs, there are opportunities for alternative development, at lower prices. Such a parallel drug development line would exist in parallel with the industry and does not force the industry to change their modes of action or habits. In order to make this possible, several building blocks need to combined:

2 Introduce independent validation of clinical trials

7 Fund comparative effectiveness research

10 Subject new drugs to a requirement for therapeutic effectiveness

Discussion

Similar initiatives have evolved in the field of neglected diseases etc. These examples proof that it is possible to develop drugs at lower costs. The main challenge remains sustainable financing: the payers need to be convinced that investing in this type of alternative R&D approaches is beneficial on the long term because the end products will be less expensive.

If the parallel track leads to successful and affordable innovation, the pharmaceutical industry will need to 'jump on the wagon' and also develop drugs in a more cost effective way.

One of the reasons that drug prices with this system will never skyrocket is the absence of IP rights.

Complementary to this, a EU licensing system should be developed that specifies exactly what is considered as patentable, because we have a history that minor modifications, without a real innovative step, are put under patent and are being fiercely protected by the industry.

The attractiveness of this system is that it can be gradually introduced and implemented. On the short term, it is not disruptive for the existing system, but if successful, it can become a major game changer.

Why does it not already exist today? Isn't the main problem that successful academics and not-for-profit research institutes nowadays get offers they can't refuse for their breakthrough inventions? Currently universities and public research centres are partially financed by selling off their knowledge.

So there is also an aspect of governance of public research centres in this story.

Public research centres should enhance their medicinal chemistry expertise and capabilities in order to produce therapeutic grade molecules. Otherwise this scenario is not viable. On the other hand, industrial partners will probably join the system to deliver expertise and production capabilities to deliver therapeutic grade formulations of molecules developed by the third track.

Appendix 3.3. SUBGROUP 3

Seed scenario 3.1

Alignment of R&D incentives with public health needs

The discussion started out as an aspirational exercise with first a mapping of how decisions are made at different stages in the discovery, development, regulatory, pricing and reimbursement processes. The idea was to identify the crucial infliction points at which to intervene by making evolutionary and/or revolutionary changes.

At some point the discussion ran aground on incentives and financing of research and development, the dynamics and constrains of the current licensing system, intellectual property rights, ownership etc.

However, the group came to some interesting suggestions for solutions, driven by a number of the building blocks.

The fundamental assumption of this scenario is that the intensity of research and the way, in which it is funded, has a significant influence on the price of the end product. So this scenario, and the discussion in the group, was focused on alternative R&D incentives. Although it is clear from the current situation that R&D intensity is certainly not the only factor influencing drug pricing

Key drivers

The starting point of a possible future scenario that *aligns R&D with public health needs (22)* consists of two key drivers:

- Therapeutic needs
- Opportunities derived from research (independent from the source – public funded, private, ngo, collaborative, …) leading to targets, candidates, molecules, and eventually products.

The discussion group pointed towards 8 building blocks that are critical to make the necessary changes:

1 *Increase transparency in drug development cost, priority setting & pricing (+ B)*

2 *Introduce independent validation of clinical trials.*

7 *Fund comparative effectiveness research.*

10 *Subject new drugs to a requirement for therapeutic effectiveness (avoid surrogate endpoints).*

15 *Find alternative ways to compensate R&D efforts that allow to modulate exclusivity rights at the market access stage (decoupling).*

16 *Support a competitive, transparent research infrastructure that de-prioritizes ownership.*

19 *Refocus and revamp international treaties in favour of public health and equity.*

22 *Align drug development with clear health priorities*

Research and pricing

The critical overall building blocks are 1 and 22. Transparency on cost, pricing, and priority setting is essential in a scenario that wants to focus on aligning R&D with public health needs. Furthermore, international treaties (19) need to be adapted to make these changes possible. Also de-linking high prices from the development cost (15) and the setting up of an alternative R&D infrastructure that de-prioritizes ownership (16) are important.

The group did not specify exactly how ownership should be regulated, but for them it was clear that the current system of patents and licensing was not the most efficient way to deal with ownership, especially not in a context of aligning drug development to public health needs in an affordable way.

All building blocks that have to do with public trials (2,7, 10) should also be integrated in this scenario.

Seed scenario 3.2

Towards a European political agreement to cap profits of health care industry.

The group felt the need to develop a feasible scenario that can be implemented in a relative short time period. The aim of this scenario is to retain the possibility for industry to continue to innovate, while ensuring that the prices for new drugs remain reasonable and affordable for societies that have built their health systems on solidarity.

Crucial building blocks for this scenario are:

1 Increase transparency in drug development cost, priority setting & pricing

B Create transparency on payers' priorities and willingness to pay.

4 Centrally assess clinical value (4a) and price of new medicines (4b)

6 Adopt value-based pricing based on principled negotiation processes

Transparency

The first building block is to increase transparency on pricing, development cost and priority setting (1+B). Transparency is needed from both sides: the developers and the payers.

Assessing clinical value

The second building block is the need to assess clinical value and other health technology assessments at central level by a European Agency (4a). This should be feasible in the next 3 to 5 years. (see Joint Action 3 of EUnetHTA)

After such an assessment, it would be possible to enter into a kind of a principled negotiation process about pricing (6).

The profit issue

The extremely high margins and profitability currently made by pharmaceutical industry are no longer accepted. A sort of limiting cap on profits will be introduced, but at the same time the incentives on successful R&D will be high enough for the industry to continue innovation. For this to happen, the group proposes some kind of 'Cost +' mechanism (cost of R&D, + cost of manufacturing, +…) to establish the final price. Since price negotiations are operationalized at national level, there will be more or less an incremental implementation of this scenario. Such an incremental implementation should make the scenario more feasible.

Discussion

In principal this change has to be embedded in the EU legal framework. In practice, this should be started, implemented and operationalized at the national levels, more or less on a voluntary basis.

The basic axis of this scenario is value-based pricing. It is not clear, however, apart from introducing the cap on profit, how a value based system would lead to more affordable innovative drugs. Especially in a system were clinical trials are not conducted independent from industry. It would be very difficult to control prices with such a value-based system.

According to some participants putting caps on profitability of a whole sector, whether at national or at supra-national level will never work. It is unfeasible. Others however argue that the UK, with the Pharmaceutical Price Regulation Scheme (PPRS), shows that this scenario is feasible.

This is essentially a cost ++ system. But the problem is that the costs made to develop and produce a drug are not reflected in the ultimate pricing. A company that has developed and produced a hugely expensive drug, might not see these costs reflected in the price if the added value, in terms of QALYs for example, is limited. Therefore an incentivising model to reflect truly added value should be developed.

A way to deal with this issue is to think along the lines of portfolio added value pricing, with modulation of the prices (downwards) for products that are 5 to 10 years on the market. This would make place for new products with high value.

Appendix 3.4. SUBGROUP 4

Seed scenario 4.1

Non-exclusivity + new incentives

A public health needs driven system, based on non-exclusivity and new incentives for R&D and innovation, starting with therapeutic areas of market failure and areas with unmet medical needs.

The scenario consists of three major steps:

Needs and prioritization

First, the health needs are defined and prioritized, both at global and more regional level. This could be an exercise conducted by a government or a consortium of governments, but could also be done with input from private players. Building blocks are:

21 *Develop foresight capacity.*

22 *Align drug development with clear health priorities.*

24 *Create clarity on what our societies expect from our health systems.*

C *Preserve independence from commercial interests of institutions, regulators, and health professionals dealing with drug development, pricing and purchases.*

Incentive development/revise exclusivity rights

Secondly, new incentive models need to be developed to encourage R&D. These models would no longer rely on market exclusivity rights.

15 *Find alternative ways to compensate R&D efforts that allow to modulate exclusivity rights at the market access stage (decoupling).*

16 *Support a competitive, transparent research infrastructure that de-prioritizes ownership.*

Transparency and evidence development

Requirements in this system are enhanced transparency and raising the quality of the evidence.

2 *Introduce independent validation of clinical trials.*

7 *Fund comparative effectiveness research*

10 *Subject new drugs to a requirement for therapeutic effectiveness (avoid surrogate endpoints).*

23 *Educate and empower patient/citizens and preserve their independence from commercial interests.*

C *Preserve independence from commercial interests of institutions, regulators, and health professionals dealing with drug development, pricing and purchases.*

E *Back up post-authorization real-life use monitoring of accelerated market evaluation with un-biased evaluation of safety and efficacy trials.*

Who could fund this system and how? There are many possibilities. It could be one single government or a consortium of multiple governments, but also regional of global funds.

Possible performance indicators could be:

- Number of drugs with therapeutic advantage that came through the pipeline
- Trend in R&D costs
- Public procurement costs
- Effective access for patients - performance measures
- Generic competition (number of competitors)

Seed scenario 4.2

Accelerated access

Promotion of accelerated access to medicines for unmet medical need.

This scenario was not fully developed.

This scenario is based on adaptive licensing, which is to some extend already developing, but which should be well defined and restricted to areas with high unmet medical needs and in which it is difficult to generate evidence quickly.

Building blocks are:

1. Engage in early dialogue (binding or not) to collaboratively assess effectiveness and pricing.

A Monitor real life use with focus on evidence and guidelines development.

Adaptive licensing should go along with adaptive and flexible pricing in order to modulate the price based on remaining uncertainties/the level of evidence (building block 8). Within the group there was no consensus on the method of setting the price. Some were in favour of real value based pricing (but different from how it is used now), others were in favour of completely abandoning this idea.

The performance measures will be the compliance of the manufacturers with the requirements set in the framework of the adaptive licensing in terms of evidence development after approval and the time to market for these new medicines.

There should be more enforced control of these requirements. One has to make sure that the companies respect the use restrictions in real life. In case of non-compliance the drug can be retracted. Currently there is great concern about the reliability of post market trials conducted by the industry.

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