



Access to the medicine market—we could do better!

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How does a patient gain access to a medicine?

Medicines are meant to make patients better or to keep them healthy, therefore they need to be able to gain access to them: ‘How do we bring the best medicines to the market as quickly as possible in order to get the best possible result, thereby giving value for the patient?’ To be effective: that is, for a doctor to be able to prescribe the treatment and for it to be reimbursed, it is necessary, irrespective of indication and related patient potential, that the treatment has been proved effective and has better results than a placebo or is not worse than an existing medicine (the so-called non-inferiority-principle (1). To get this ascertained and approved a potential medicine has to follow a one-size-fits-all route with generally the same procedures and criteria.

Industrial research

After the preclinical route, the impact and effectiveness of the medicine has to be tested with people. Medicines are stable molecules that have to be examined before they can be accepted for general use. Molecules are mostly developed in an academic and biotech environment and after stage 1 or 2 they are bought by industry. When industry expects the new molecule to be successful, clinical research is defined in trials. In general, the established pharmaceutical industry itself does relatively little high risk fundamental research (2).

Trials (3)

- ❖ A stage 1 trial is set up and carried out to determine a safe dosage.
- ❖ A stage 2 trial is set up and carried out on a small group of patients to determine if the medicine is effective.
- ❖ A stage 3 trial is set up and carried out to affirm the

effectiveness in a large(r) group of patients and to trace side-effects. The size of the group depends on the illness. You may wish to have 400 melanoma patients with a BRAF defect in your trial, but it would take too long to fill the trial.

- ❖ A stage 4 trial (the evaluation stage) is executed after market access. Via phase 4, more information is obtained about the use in daily practice. This can lead to a more precise use of the drug. The effect and the side effect of drugs in daily practice can sometimes be different from that of clinical research. This phase is also used to evaluate the effectiveness of the drug with respect to price, risk or side effects. Furthermore, phase 4 observational studies (e.g., registries) are also used to better understand the effectiveness of new and existing medicines in real-life settings regarding individual patient characteristics. Such phase 4 studies are generally not conducted on a voluntary basis, and they are generally reimbursed. A phase 4 trial is little used.

Regulatory assessment

This set procedure ensures that the medicine meets with ‘the State of Science and Practice’ where evidence-based medicine (EBM) is important. This principle is applied to determine whether the drug can be licensed for trade in Europe by the European Medicines Agency (EMA) and in the United States by the Food & Drug Administration (FDA) and also to be put on the list with medicines for reimbursement. If it is reimbursed, it can be prescribed by a doctor. EMA will adhere to EBM principles, but it does not make decisions on reimbursement. That is the task of national institutes and eventually, the Ministers of Health. It is essential that EMA and FDA apply the rules and do not make them. That is what governments in Europe and the

United States do. Health Technology Assessment groups to inform on reimbursement decisions are the task of National authorities. Generally the Minister of Health will decide upon reimbursement status based on an advice from a National reimbursement authority.

Trade license

The industry has to comply with the rules of the regulators to get a trade license for its medicine. A license is required in order to market it and for it to be eligible for reimbursement. Licenses are requested from the judging institute (EMA or FDA) after successful research with positive results. The request is made by the industry, but has to be accompanied by research data from clinical testing (and often from preclinical research as well) and are supplied by researchers and doctors (4,5).

The route to the patient

If the medicine is available and the price is determined, doctors can then prescribe it for the illness for which it has gained the license and then it is reimbursed. In general doctors wait for the development of guidelines by their occupational group (each group does this per individual country, with differences between the countries). Prescribing is also allowed for other illnesses than the ones for which a medicine is registered. Then it is called 'off label' and it can still be reimbursed, but a health care insurer is not obliged to follow suit. In general, the healthcare insurer does not cover costs for expensive cancer medicines and hospital budgets also cannot cover the costs. Doctors who want to prescribe more expensive medicines are dependent on budget holders and hospital management. Decisions on that level could lead to serious consequences for patients concerned.

What goes wrong?

There are a number of questions to be raised regarding access of medicines to the market that relate to the objective (phrased by me after conversation I had with stakeholders in the medical industrial complex over the last few years): 'How do we bring the best medicines to the market as quickly as possible in order to get the best possible result, thereby giving value for the patient?'. We ignore the distinctions between tumors; there is no pure evidence-based medicine; trials do not serve the patient; quality of life is not being

considered and patients do not play a role in decision making. This applies to market access and also to the evaluation of the effectiveness of medicines that is limited to default. In all, we can state that the medicines market is complex and therefore, cannot work in the same way as other markets.

We ignore the distinctions between tumors

It matters if you are diagnosed with lymphoma, pancreatic cancer or glioblastoma. Lymphoma has a high survival rate and protocols are effective in many cases. There is still room for improvement, but this will take place in small steps because we already offer so many patients longer, good, happy and healthy lives. For pancreatic cancer and glioblastoma the protocol does not work. Therefore, we must change procedures for these tumours in order to stimulate acceleration of research and introduce treatments that are effective and offer long term solutions for patients. Continuing along the current path will not lead to a solution.

There is no pure 'evidence-based medicine'

There is a lot of controversy around evidence-based medicine. This is not what the founder of the evidence-based medicine, David L. Sackett, meant with evidence-based medicine. His definition (6): 'Evidence-based medicine encompasses the integration of clinical expertise with the best available external evidence alongside with patient preference'. It is wrong that patients and doctors are not listened to when a medicine is judged. Doctors have years of experience and see hundreds of individual patients with heterogeneous profiles. It won't be the first time that a doctor says: 'If I look at the data alone, there is not much wrong with the patient, but in reality, the patient might be really sick.' Statistically, results can show improvement but the patient, themselves, may hardly benefit.

Trials do not serve the patient

Trials were not designed to benefit the patient. The way in which trials have been developed is for the benefit of access to the market. The inclusion criteria have led to the situation that the group of patients in the trial is often not representative of the patients who get the medicine after market access. Dana Faber physician, Deborah Schrag, phrases it as follows (7): 'Clinical trials are Fake World

Evidence. As an example, the average age of patients in a colorectal cancer trial is 55, but the average age of my patients in clinic is 71. The clinical trial results aren't really relevant to my decision making for my patients'. People are hindered by inclusion criteria that exclude them from the trial. Apart from the fact that we don't allow them the chance of a trial, we also don't find out the clinical result of supplying the medicine to a different group than in the trial. For that is what happens. Trials seldom take place in representative groups and outcomes are therefore difficult to transpose to what could be expected from treating the eligible population. What we have made happen is that a process that is good in itself, e.g., testing medicines in stages, has grown into a process to provide a trade licence for the medicine. How do we expect patients to become enthusiastic about stepping into a trial, when practice shows that trials are not there for them and doctors/scientists like Deborah Schrag (she is not alone) confirm this with evidence?

Quality of life does not play a role in judgment criteria

Patients with cancer of the colon metastasized to the liver can be treated with a standard operation or through intervention radiology (via the vascular system an intervention radiologist goes to the tumor, guided by MRI, and removes the metastasis). The standard operation leads to a 7 days' hospital stay and a 2 to 3 months' revalidation. Intervention radiology leads to a one-day hospital stay and no revalidation. Apart from the expenses the quality of life is much better, but the 'overall survival' does not improve. Overall survival is the primary endpoint, meaning that treatments should result in statistically significant improvements for a treatment looking at this endpoint. This is more specifically the difference between the time a patient lives with the new medicine versus survival without the medicine (but with standard of care or placebo). Clinical phase 3 studies are set-up according to formal guidelines and rules, describing – among other aspects – the number of patients included and the time scale in which to reach conclusions. Another end-point is 'progression free survival': how long does the patient's illness remain stable and not get worse? Thus, there are a number of types of primary end-points that are valued differently, but 'quality of life' is generally not valued as an endpoint or may only be included as a surrogate or secondary endpoint, whereas, for patients, this is very important. Enquiries at ZINL (Netherlands) and EMA teach us that leaving out 'quality of life' is also thought to be wrong by them. These rules simply have to

be applied and the rules are made by governments (EU or US government). It is recognized that patients and patient organizations have to indicate the criteria involved when we speak about quality of life. What is quality of life? The terms have to be defined by patient advocates.

Patients do not play a role in decision making for market access

Patients are listened to in many fields, but where decisions about market access are concerned, they play no role. This is not right, because this is concerned with whether a medicine works or not, whether it offers a better quality of life and also about the risks of the medicine. The people who make the decision do not have to take the risk in receiving the medicine. The patients do. That is why the patients have to be involved in making these decisions. We are worried because ineffective medicines remain on the market. Patients do not want medicines that do not work. These are supposed to be taken off the market after stage 4. But then, this has to be done!

Medicines are hardly evaluated

Phase 4 study or post-marketing surveillance is for safety monitoring as well as for measuring effectiveness. This phase gives the opportunity to see whether conclusions from phase 3 are justified or not, whether there are unforeseen side-effects and any potential additional effects. Reporting of severe side-effects can lead companies to take the medicine off the market or at least, restrict indications to smaller groups of patients. In practice, this rarely occurs because of the rigorous marketing authorization process. This is very important, since it is increasingly becoming more and more clear that certain medicines do not work for (all) patients. In the Netherlands, research into this has been conducted by physician and epidemiologist Dick Bijl (1), internationally by John Ioannidis (8,9). It is true that there is always a selection of patients for whom it does work. That is why it is difficult to stop treatment and reimbursement and remove a specific medicine from the market.

The medicine market is no normal market

A market has consumers and producers and the consumer pays the producer for the product that is bought. There is a supply and demand mechanism, in which the consumer creates the demand. With the healthcare market it is not

the patient but the healthcare professional who determines what type of healthcare the patient receives. Furthermore, the consumer generally does not have to pay for the healthcare offering, depending on the country in which the patient lives. 'Healthcare is like dogfood business'. A dog does not pay for its food and neither does it determine what it gets. This is no small difference. A normal market has consumers that enforce what comes on the market and what is paid for it. That is why the patient has no direct say about the introduction of new medicines to the healthcare market. There is so much room for improvement (10).

What has to be done?

The changes that bring us closer to the objective, 'How do we bring the best medicines to the market as quickly as possible in order to get the best possible result, thereby giving value for the patient?' are: do not use the process-based approach of ignoring all distinctions between tumors, continue the development to precision medicine with full force, introduce value based healthcare and most importantly, involve the patient in the decision making process.

Do not use the process-based approach of ignoring all distinctions between tumors

Changes are necessary to speed up the process of getting medicines against pancreatic cancer and glioblastoma to the market. At the moment, it takes far too long and with little to no result. In order to do this:

- ❖ Provide the best diagnosis: pathology, imaging, whole genome sequencing and proteomics. Introduce new techniques and implement these to identify and treat patients eligible for successful therapy. Some of the new techniques might not yet be at the required level but together the above mentioned techniques for diagnosis are better by far than the way we diagnose today.
- ❖ Bring together the agreement between treatment and reimbursement.
- ❖ Register what treatment patients receive and how patients experience the treatment pathway.
- ❖ Share this with healthcare professionals all over the world (patients want this and probably want to demand this).
- ❖ Learn from your experiences and those of your colleagues.

Compensation is essential. Medicines are too expensive to experiment with at the expense of hospitals. This has to come from the industry (for medicines that have not yet been registered) and from health care insurers (for registered medicines). At present [2018], there is an initiative in The Netherlands to make this possible. Thoughts are given shape and possible measures discussed. However, let it be clear that the most complex illness cannot be cured with only one method. Tumors with hardly any survival have to be approached differently from tumors with a long term survival.

Continue the development to precision medicine

Precision medicine is the future hope for patients. 'Breast cancer' does not exist as one disease. We know that a BRCA-mutated breast cancer occurs in tens of thousands of variants. These are registered in the databases of Global Alliance for Genomics and Health (11). This means that Olaparib can be effective or not effective, as in many cases. We can define this more accurately all the time as we get closer and closer with better and better diagnosis. Precision medicine is not a new treatment. It is an innovative approach of identifying the right patient for successful therapy. Individual patients, with his or her genetic defect, should be able to get a custom-made treatment based on early and continuous diagnosis. This cannot be achieved in the way we are currently treating patients. That is why we have to adopt a different approach, set up the process differently and make it efficient. The car industry is able to supply a custom-made car per buyer and to gain much revenue and profit in that way. This individual approach can also be implemented in health care.

Introduce value-based healthcare

There is a lot of discussion about value-based healthcare and sometimes it seems to be on firm ground. It is all about the 'value' for the patient. Many medicines are either hardly effective (1,8,9) or have so many side-effects that the quality of life seriously decreases for the patient. This is why it is important to think about 'value', to discuss it and to make decisions together with patients (shared decision making). In my opinion, value is measured by the patient's opinion and the doctor's assessment. Together they are able to say something sensible about this value. This is why we should start with the patient when determining this after their

consultation with their doctor when they are well informed about the potential added value. ‘Informed consent’ plays an important role here. It is of great significance that patients indicate what they see as ‘value’, what treatment they want and what risks they are prepared to take.

Involve patients in the decision-making process

It is not correct for patients to play a minor role. It is all about them and they are hardly involved in the decision-making. Of course, they are asked about their opinion, but the decision is made by others and this, while we are talking about treatments that can save their lives and about risks patients are subjected to. Doctors, industrialists, bureaucrats, lawyers, health care insurers and politicians: the whole ‘medical industrial complex’ decides about treatments, expenses and risks for patients. This is the reason why healthcare is a market like no other market. ‘Healthcare is like dogfood business’ (10). Patient advocates are perfectly capable of discussing research, treatments, trials, risks and more. I understand that healthcare stakeholders see a different picture of the patient. Patients depend on their doctor and give the impression not to be able to share in the actions mentioned. They are unstable and badly informed, especially in the first few months of their diagnosis and treatment and because of this, we get an image of patients unable to discuss and decide. But patient advocates can. They are well-educated and capable of acquiring, interpreting and valuing difficult information. They are molecular biologists, radiologists, physicians, general practitioners, lawyers, et cetera. Just as in the period of the Aids activists, there are patient advocates in the field of cancer research and treatment. They are capable experts. We have to get used to it, but if you, as a stakeholder in the medical industrial complex, become used to cooperating with patient advocates and making decisions together, you will find yourself in a situation that contributes much more to the quality of your treatments in that way and improve the quality of life of patients and their loved ones. This win-win situation is a possibility and would bring about an improved quality of care and most likely, also, a decrease in expenses. It is clear: no patient is waiting for a treatment that does not work and we know that unnecessary over-treatment occurs (1,8,9).

What problem can we solve with this?

We have seen what does not go well, reasoning from

the objective: ‘How do we bring the best medicines to the market as quickly as possible in order to get the best possible result, thereby giving value for the patient?’. What problem can we solve when we do what has to be done?

By introducing the patient to the medical industrial complex, evidence-based medicine will be used as it was meant. The patient is heard, becomes part of the justification of the treatment and supplies proof of it as well. Patients will take their ‘partners in crime’, the doctors, with them in the decision-making process. There will be a correct consideration of hard data as proof, next to the doctor’s clinical judgment and the patient’s narrative; this to avoid the opposite signals from data that say that the patient’s condition exceeds expectations, whereas the patient, in essence, is a very sick bedridden human being. It is also essential that the patient cooperates in gathering real-life data that provide proof that the medicine is effective in the long(er) term. This is the responsibility of the patient and they will take it. Medicines can reach patients and the market quickly and stay there if they are effective. If they do not work, they can be taken off the market.

We get a more normal market when it is the consumer that determines it. The treatments that are the result of the decision-making, whether it is the trial that determines if a medicine is admitted to the market or the treatment that has to be given on the basis of the diagnosis, the patient has been at the helm and is responsible, together with the doctor. This is as it happens in a normal market. If I prefer Pepsi Cola instead of Coca Cola, I choose Pepsi Cola. On the basis of good and reliable information, the patient decides about a treatment from evidence-based medicine, and with informed consent, he is aware of the risks. This is the reason why the treatment has ‘value’: this is value-based healthcare. Besides treatment, compensation stems from this value as well. This is a requirement and a consequence. A treatment that has no value after evaluation (when no one or hardly any patient benefits from it) will not be covered by reimbursement schedules and will disappear from the market, or with proven ineffectiveness a product can be withdrawn from the market.

By involving the patient in the plan and decision-making process trials will be set up differently. When they have more ‘value’ for the patient, it means more patients will step into the trials and ask for them. It is essential that patients ask for an extra ‘endpoint’ at the trials: quality of life. Strictly speaking, this is possible right now but because patients are rarely involved in the decision-making process, this does not happen enough. When a new treatment does

not offer a longer survival, but does improve the quality of life, patients will ask for this new treatment. Do bear in mind that this means a considerable reduction in costs. Better quality of life means less cost in fighting side-effects.

When we evaluate medicines in a different way with distinctions based on tumor types, cancer types (e.g., pancreatic cancer and glioblastoma) we increase the possibility of gaining faster access to medicines: testing each patient with medicines fine-tuned to that individual patient. Clinical studies can be done faster when we share the results with other countries and also see their results. ‘Learning by doing’.

The choice of medicines for tumors with an ‘unmet medical need’ is extended to all registered medicines and these are compensated by the health care insurers. Medicines undergoing study in phase 2 clinical studies can also be added to the treatment options and will be made available and compensated by the industry. This form of accelerated access will reduce investment in big phase 3 clinical studies and can therefore lower the price. For these indications, patients are willing to take a lot of risk as they know that the only alternative is to die from the cancer. Grant and give them this medicine and the opportunity to help in the research for better methods of treatment. It is often the only thing they can do and they are happy to help (12).

At last

The text above is a plea for precision medicine with the patient at the forefront. We are only able to talk about precision medicine if we implement this patient-centered approach with the patients in the drivers’ seat. Never say that it cannot be done. Or to quote Pippi Longstocking: ‘I have never done it before, so I think I can do it’.

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