A Healthy Sense of Trust

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Abstract
In the fast-moving arena of modern healthcare with its cutting-edge science it is already, and will become more, vital that stakeholders collaborate openly and effectively. Transparency, especially on drug pricing, is of paramount importance. There is also a need to ensure that regulations and legislation covering, for example the new, smaller clinical trials required to make personalised medicine work effectively, and the huge practical and ethical issues surrounding Big Data and data protection, are common, understood and enforced across the EU. With more integration, collaboration, dialogue and increased trust among each and every one in the field, stakeholders can help mould the right frameworks, in the right place, at the right time. Once achieved, this will allow us all to work more quickly and more effectively towards creating a healthier – and thus wealthier – European Union.

The Age of Regulation

From man’s earliest ventures into healthcare, when shamans, priests or medicine men ministered to the sick, trust has been at the centre of the compact between patient and carer. People at their most vulnerable moments choose to place themselves in the hands of others, in the confidence – or at least the belief – of benefit and relief.

That compact remains just as valid in today’s world of science and technology. The rapid development of medicine in the last 50 years, and more particularly the exponential leaps of
the last 25, have created opportunities unimaginable only a couple of generations ago. Genomics is increasingly permitting a focus on the underlying nature of disease – and the underlying processes of health.

It is generating knowledge that is unprecedented both in terms of the detail of individuals’ characteristics and in terms of the sheer volume of data about populations and sub-populations. As a result, at one end of the scale there is a growing ability to treat smaller populations – with orphan drugs for rare disease, or validated paediatric medicines, or advanced therapies, and with an unfurling range of possibilities as personalised medicine evolves. And at the other end of the scale health authorities begin to tap into a wealth of information about health trends, susceptibilities and the value of distinct treatment options that can radically improve health systems management.

So the trust invested in the shaman is even more crucial today. The emergence of evidence-based medicine and organised health services that are overseen by governments entitle patients to a degree of certainty that their best interests are being attended to on the basis of reason and equity as well as of faith [1]. And in Europe, the interdependence of Member States makes it both necessary and desirable that much of that task of oversight is organised at EU level.

It is, inevitably, of course, a more complex compact nowadays. Each component of the systems on which people now routinely depend for their health has to fulfil its part of the bargain. That isn’t just a matter of doctors discharging professional responsibilities in return for salaries, or hospitals maintaining the highest standards of hygiene and care-quality, or researchers maintaining scrupulous rigour in their analysis of data. Governments, as the ultimate guardians of the public, must legislate and regulate to ensure appropriate standards and behaviour – by the providers of healthcare service, and just as crucially, by the providers of healthcare-related goods [2].

So to prevent contamination in the food chain, systems of inspection and control from farm to fork are created and constantly developed. Advertising and information about products and services must respect agreed values of honesty. And any offer of therapy or therapeutic substance or procedure or device is subject to tight requirements [3].

In other words, we live in an age of regulation, where regulators have taken on a crucial role in articulating the equation of trust between healthcare suppliers and patients.

In a perfect world where nothing changed, that would be enough. But of course the world is not perfect, and circumstances do change. So to make the world as perfect as possible, everyone in a position of responsibility has to keep reviewing how they do things, to make sure the results are as good as possible, and that the principles and values of protecting the patient are optimally defended. And everyone has to keep making adjustments where necessary [4].

This applies to regulators and to the regulated.

Regulators recognise this clearly, and regulation is constantly reviewed and adjusted. Necessity has been the mother of invention for regulators. From the thalidomide tragedy and the trigger this constituted for modern drug regulation, there has been a steady – and sometimes even spectacular – growth in regulatory oversight. The adjustments have seen EU legislation cover the quality, safety and efficacy of medicines and extend into innumerable other aspects of drug development, from GCP inspections to combating fakes [5].

Without such adjustments, the credibility of regulators would be at risk. But over-rigid rules can be as harmful as rules that are too slack or inadequately enforced. That is a balance that requires constant review and adjustment, to ensure that attention is focused on the appropriate issues as science advances – as current reflections on adaptive approval demonstrate in the age of big data [6].
Galileo ran into real problems from the stubborn regulatory climate of the late middle ages that refused to countenance change. If Isaac Newton was to come up with his proposal of the theory of gravity today, would he too encounter bureaucratic obstacles based on failures to grasp the essence of the challenge? Would he have to satisfy innumerable local requirements for his theory to be accepted and applied in a region – or EU wide? Would regulators demand that he test his theory with different types of apples, to preclude varying effects of gravity on Golden Delicious or Granny Smiths? Or would he be obliged to produce data on the phenomenon observed at different times of the day, or different seasons of the year? Would regulators seek additional evidence from trials with other fruit – a pumpkin perhaps? (With, of course, due caution from health and safety authorities to prevent any risk of head injuries sustained by researchers from falling pumpkins.)

The key factor in regulatory credibility is the relevance of the regulation. Intense scrutiny focused on the wrong aspects of a phenomenon inevitably weakens credibility, raising questions about the need for such a level of scrutiny. It can appear, at worst, to be a search for the fifth leg of the cat – or for compelling evidence that the cat does or doesn’t have a fifth leg. So successful regulators have to win public respect by the demonstrable relevance of their activity, as well as by the more obvious factors of the accuracy of their information.

But on information too there are heavy responsibilities for everyone involved. And in the world of medicines regulation, much of the information required for making decisions comes from the clinic and from clinical trials [7].

**Accuracy and Accessibility of Clinical Data**

The public debate on availability and accuracy of clinical data has become increasingly lively over recent years. Regulators have been accused of failing to take account of data they should have reacted to. The Mediator case in France demonstrates how wrong things can go when signals are ignored. For years, adverse reaction data to a medicine widely mis-prescribed off-label was not compiled with sufficient rigour, with the consequence that many patients suffered serious side effects and patients died. And over decades, medicines have had to be withdrawn after side effects contradicted initial enthusiastic regulatory endorsement [8].

The debate extends also to access to data – and particularly clinical trial data [9]. There have been longstanding demands for better data and better access to data from public interest groups and invertebrate critics of drug regulation, dating back to before the 1980s. Ralph Nader’s Public Citizen movement in the USA found its echo in Europe with the Social Audit movement run by Charles Medawar or the Drug and Therapeutics Bulletin of Andrew Hershheimer in the UK, or Prescrire in France, or the work of Silvio Garattini at the Mario Negri Institute in Milan.

Since then, and with the impetus reinforced by health activist groups such as Health Action International or research groups such as the Cochrane Centre, regulators have moved both to strengthen their database of drug information, and to share it more widely. Refinements of the EU procedures for marketing authorisation have given new emphasis to safety reporting, and enhanced pharmacovigilance rules in the EU impose much tougher requirements on drug firms and doctors to flag up adverse events [10]. The European Medicines Agency, prompted by rulings from the European Ombudsman, has progressively eased access to clinical trial data filed by companies, and in the last five years has made big strides towards systematic public access to data in its possession. At the same time, the EU has legislated to open up to public view information about ongoing and upcoming clinical trials, and to put in place a portal to centralise all this information – now deferred until 2019.
But there is still dissatisfaction over the quantity and quality of data available for decision-making. Yannis Natsis of EPHA says “it is critical to guarantee that HTA bodies have access to more and better clinical trial data so that their assessments are based on solid evidence” [11].

Controversy still rages over whether publications of clinical trial findings accurately represent the reality, with the scientific media swept up into discussions of bias and selective reporting. This too is having clear consequences, in a widening wave of protestations and commitments from trial sponsors and editors determined to demonstrate their probity [12].

Inevitably, as components of a living system, regulators are continually – and appropriately – adjusting their behaviour and their operating rules in a bid to obtain the best outcome for the public interest that they serve. By their nature, they are condemned and empowered to operate at the junction between the ideal and the feasible, the known and the uncertain.

Dealing with Uncertainties

They are faced with new uncertainties that they have to find ways of coping with in respect of another novel trend – repurposing of existing drugs for new indications. The EU expert group on safe and timely access to medicines (STAMP) has been reflecting on this challenge over the last couple of years. While new indications for well-established off-patent medicines in areas of unmet medical need could offer additional therapeutic options to patients, it says, the subject needs careful handling. In discussion with stakeholders, the authorities have been exploring whether the clinical evidence generated for regulatory decision-making adequate for subsequent decision-making – on issues such as pricing and reimbursement, and whether the right opportunities exist to discuss and agree evidence-generation plans for repurposing “across all relevant decision makers” [13].

A number of balances have to be struck. Obviously, between opportunity and considerations of effectiveness and safety. But there is also a balance to be struck in respect of rival claims for resources. This is not just an issue for safety regulators, but also for the authorities that make decisions on how to set research priorities and allocate funding [14]. This is a live issue that regulators have to face up to. A recent conference of the UK’s National Cancer Research Institute featured a debate on the motion “This house believes research into repurposing existing medications and optimising use of current breast cancer treatments should be prioritised above research into developing novel agents.”

Everyone in the entire healthcare sector is subject to the same responsibilities of review and adjustment. No-one is exempt. No-one can step aside from the need to win broad public support for their actions, and to be able to justify what they are doing or, where that is unjustifiable, adapt their actions. It is not just the pragmatic consequence of the internet age, where technology has given such high visibility to matters that were often discreet and even ignored or unknown in the past. Accountability is also a moral duty for any party that claims to operate in the public interest [15].

Healthcare professionals have the same duty to continue learning, as part of discharging the fiduciary trust that patients and society in general invest in them. To be able to do their job and contribute to the improvement of healthcare, they need to make sure they remain abreast of developments in their professional world and in the policy context they operate in. Many physicians cheerfully – if slightly guiltily – admit that they don’t often read about public health from a legal or political point of view, even though they acknowledge that they should learn more about it. Many also admit to a distinct conservatism about innovation – because of the insistence on total safety that has been inculcated into them in their medical training [16].
Everyone in the entire healthcare community ought to be aware of the changing context, so each can do his or her job better, and can remain alert to new opportunities for improving patient care. This does not mean that every member of the healthcare community has to know the same things – but each one in his or her own field should be keeping an eye on the bigger picture.

This applies as much to the drug industry as to any other stakeholder in health. Drug firms have to be responsible stakeholders if society is to trust them. But to gain and to keep trust, the industry too has to keep its operations under review, and adjust them where appropriate.

This is true in respect of their products and associated services. They must provide medicines that meet the demands of quality, safety and efficacy, and promote and monitor them to maximise the benefits to the ultimate consumer – the patient. If they want to retain the room for manoeuvre in pursuing innovation, they must argue convincingly with decision-makers for space to explore and experiment – whether that be in terms of conserving and accessing data or proposing modified procedures for product authorisations [17]. They have to make the case in the face of concerns such as those expressed by the Maltese presidency of the EU in mid-2017, about how patient safety “should not be compromised in order to obtain quicker products on the market.”

The European Parliament has warned that “inherent to adaptive pathways is a higher degree of uncertainty regarding the safety and effectiveness of a new medicine at the point of authorisation in comparison with traditional licensing” [18].

Maintaining credibility also applies to industry’s relations with society in general. The predominance of public or mutual financing of healthcare in Europe adds a social element to the compact that drug firms must respect. No matter how good a product is, the patient who benefits from it is not, normally speaking, the person who pays for it. The bill is picked up by society at large, through insurance or taxation. So all the members of the paying public – and their appointed or elected representatives that run health insurance agencies or health ministries – have a legitimate interest in the business side of patient care too [19].

Hence, to maintain confidence and trust from the public – and from the regulators that protect them – the industry is obliged also to take seriously the calls it faces with increasing frequency (and volubility) for greater transparency about its economics – and particularly about how it prices the products that society as a whole has to pay for.

For innovators, the challenge – and the need – is all the greater, for they have to do more than convince society of the legitimacy of the products they already produce. They also have to win support for their arguments that the research on which their innovation depends also deserves respect and assent. And in a world grown increasingly sceptical, that task is all the harder, and the efforts required all the greater, to win that campaign. Already calls for tougher action against drug firms are being heard from right across the EU, not just from activists, or from MEPs with an activist agenda, but from government ministers in the member states. The pressure grows for constraints [20].

Last year, the ambitions of the Dutch presidency of the EU to shake up EU medicines strategy were partially realised at the Health Council in June, when national health ministers backed the conclusions on bringing more checks and balances into drug pricing and reimbursement. Edith Schippers, Dutch health minister and president of the Health Council, said after the meeting “We are giving a strong political message that we need change” in the way the current drug pricing and reimbursement system is operating. This was necessary, she said, to avoid shortages, high prices, and issues of equal access to medicines. One of the main achievements of the Council meeting was, she said, that member states will continue to explore cooperation on pricing and reimbursement [21].
Price Transparency

The Council conclusions noted “with concern an increasing number of examples of market failure in a number of member states, where patients access to effective and affordable essential medicines is endangered by very high and unsustainable price levels, market withdrawal of products that are out-of-patent, or when new products are not introduced to national markets for business economic strategies and that individual governments have sometimes limited influence in such circumstances” [22].

Later in the year, Schippers and her international trade and Dutch development minister Lilianne Ploumen wrote in The Lancet that the current drug development system, based on intellectual property exclusivities, will no longer do. “We need to develop alternative business models. And if public money is used for the development of new medicines, agreement upfront is needed about what this public investment will mean for the final price. We believe that companies must provide full transparency regarding the costs of research and development” [23].

The anxieties are widely felt [24]. The Maltese presidency of the EU in the first half of 2017 highlighted the needs for “improving price transparency and narrowing the gaps between retail and negotiated prices” in advance of the Health Council. And it reported on gathering concerns among health ministers over funding of medicines. “Sustained access to medicines cannot focus solely on pricing but also on funding and hence the need to engage on how research affects pricing, and how this could contribute towards horizon scanning and new funding models,” it said. It also urged exploring how to match “the role of research” with “patient needs” [25].

Also in 2017 the European Commission set up a working group on “innovative payment models for high-cost innovative medicines” in response to growing concerns over the access problems created by drug prices and constraints of health budgets [26]. Its wide-ranging agenda goes as far as to examine if lessons can be drawn from the transport or telecommunications sectors for pricing mechanisms that can balance incentives with access. It will also examine the role of real-world data in payment systems, and whether the assessment of drugs is adequately linked to overall health system performance.

Comments from other organisations on the questions relating to drug pricing are often far less diplomatic, and would suggest that the issue is not going to go away by being ignored by the drug industry.

According to leading patient advocate Nicola Bedlington, the European Patient Forum Secretary General, “We need stronger commitment from policy makers towards a new system based on the patients’ perspective. Only a coherent framework for fair access can maximise societal benefit and patient access whilst avoiding untenable impacts on healthcare budgets” [27]. EPHA speaks of “the access & innovation crises Europe faces primarily due to the exorbitant prices of medicines” [28]. Health Action International launched a campaign backed by leading national health charities to put “soaring medicine prices” high on the political agenda ahead of the general election in The Netherlands last March [29].

Resentment has also been fuelled by a perception that the drug industry is taking money from the public purse in terms of funding for research, and then charging the public purse for the products resulting from that research. The EU Health Council pointed out in 2016 that while “both public and private investments are essential for the research and development of innovative medicinal products,” wherever public investment has played a major role in the development of innovations, “a fair share of the return on investment in such products should preferably be used for further innovative research in the public health interest for example through agreements made on benefit sharing during the research phase” [30].
Similarly, the Health Council wanted to see clearer direction for public funding of research. It urged “further investments at national and EU level in the development of innovative medicines for clearly defined unmet medical needs.” And it wanted to see funded projects involving Horizon 2020, the Innovative Medicines Initiative and the European Medicines Agency “promoting open access to research data,” and “considering conditions such as equitable licensing to ensure a fair return on investment for publicly funded research that delivered a major contribution to the development of successful medicinal products” [31].

Where to with Innovation?

To the extent that sympathy for medicines innovation is lacking, the future of medicines innovation itself is in jeopardy.

Even the drug industry’s principal European body, EFPIA, recognises that “patients can only benefit from this innovation if it is affordable now and sustainable in the future.” Because “the adoption of innovation places additional pressure on resources,” then “how we manage the rising healthcare demand and capitalise on the new medical innovation in a sustainable way is the foremost question for many stakeholders in European healthcare,” says EFPIA. It remarks with evident regret that “value-based healthcare, in which systems guide their decision based on the ratio of outcomes to cost, is still in its infancy. Healthcare systems across Europe are still grappling with how to make the concept a reality and what kinds of tools are needed to make it work” [32].

The drug industry needs to conduct its own review of its policies in these sensitive areas, and make adjustments where that would serve the overall objective of promoting innovation and benefiting patients. And if that requires some movement on how it argues the case for industry economics, then that must be done. If not, the risk is that the pressure may become irresistible for hard law to be brought to bear to control drug industry costs – and impact therefore on the sector’s capacity to innovate [33].

Innovators have to win the credibility that will allow them to operate in a regime of soft law so that they can continue to develop innovation. For drug firms, this could mean that shareholders need to have a view of the core purpose of the company to balance their desire to maximise profits and dividends. A return on investment need not mean that shareholders forget that they are also stakeholders [34].

According to Amanda Adler, a Cambridge physician who chairs evaluation meetings at NICE, “The government has an obligation to the taxpayer to only pay for stuff that actually works. It also has an obligation to the taxpayer to only pay for stuff that reflects good value for the money. NICE might see a new treatment that’s twice as good as anything we have, but we might say no if the company wants to charge ten times what is paid for a product that already exists” [35].

The atmosphere is not helped by conspicuous examples of high prices with highly questionable justification. Specialists in infectious disease were appalled by a gigantic overnight increase in the price of a 62-year-old drug that is the standard of care for toxoplasmosis. Daraprim was acquired in August by Turing Pharmaceuticals, a start-up run by a former hedge fund manager. Turing immediately raised the price to USD 750 a tablet from USD 13.50, bringing the annual cost of treatment for some patients to hundreds of thousands of dollars. The price of EpiPen, a user-friendly tool for delivering epinephrine for severe allergy patients, skyrocketed from around USD 100 to over USD 600 after Mylan bought the rights to the treatment, and sparked severe criticism of the company and its management [36].

By contrast, Regeneron voluntarily set a low price for its Dupixent treatment for a rare skin condition that causes constant itching, and won wide praise from payers – if not from its
shareholders – for the decision. The company's CEO, Leonard Schleifer, has become an outspoken critic of the pricing policies of his peers in the industry. "It's ridiculous. I hate us also when I see all this stuff," he told them at a health summit in December. "The attitude can't be that this is an impossibly hard business, so any price is a fair price" [37].

More moves like this by drug industry innovators could obviate heavier-handed intervention by authorities to impose limits on drug prices. EFPIA's 2017 slogan of "We won't rest" has been designed to highlight the industry's research commitment. But the commitment not to rest might just as well be applied to a bid to develop a better understanding in the outside world of what the industry is doing, and why it is justified in asking a price for it [38].

Industry will have to get a message across that persuades legislators, regulators and the general public that it needs a space to conduct its research. And to do that it will have to show that it is playing fair with the other stakeholders in healthcare, and is responsive to soft law signals. Soft law will work in everyone's interests better than hard law, because it will give more scope to the search for innovation. But that will happen only on condition that the innovators demonstrate a readiness to respond to soft-law signals.

**Adapt and Change**

To bring innovation to the market and to patients depends on regulation that is adaptive – and soft law and guidelines are the way to permit that adaptivity. The EU is perfectly positioned to work out how to do this. It has been a centre of innovation for more than 2000 years, driven by competition among rivals – Athens and Sparta, the Roman empire and its colonies, the city states of Venice, Milan and Florence, the voyages of discovery by Spain, Portugal, Italy, and the industrial ebullition that saw Germany, France, Belgium or the UK vying to outperform one another. For the last three generations, all this innovative capacity has flourished within a political framework that allows people to live together in peace and security. The EU is a place of continuity that depends on trust rather than force for its strength. That same trust can help ensure a brighter future for the health of Europe’s citizens by permitting continuation of innovation.

But the innovation must occur at all levels. All stakeholders will need to ensure that their own knowledge continues to evolve – and this will require a greater emphasis on continual professional training. It must involve patients more dynamically in decision-making, which presupposes measures to equip patients and carers for a more active role in their own health. And above all, it will require an innovation in the level and quality of dialogue between innovators and policymakers: in this rapidly changing healthcare world, if politicians are to discharge their task responsibly, they will have to take more seriously the need to be informed about all the implications of their decisions. And that implies that the radical change needed in healthcare systems will be made only if Europe also benefits from a radical new approach from leaders who dare to tackle health with a radical spirit.

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